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RECOGNITION AND TREATMENT OF ADRENAL CRISES IN THE NEWBORN INFANT

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ADRENAL insufficiency is one of the few generally unrecognized causes of perinatal mortality which is responsive to available methods of treatment. Its frequency is unknown, but it is certainly more common than the estimated 1 in 100,000 births. Although rare (about 1 in 250,000), the salt-losing form of adrenogenital syndrome is the most commonly diagnosed type of adrenal crisis in the perinatal period. Until the incidence of surviving males equals the incidence of surviving females, however, the diagnosis is still being missed.

This inherited inborn error of metabolism results in a crisis characterized by hyperkalemia, hyponatremia, hypochloremia, hypovolemia, and hypotension. Twenty-five per cent of the patients with adrenogenital syndrome have this type.[1-3]

The presence of the adrenogenital syndrome can be proved shortly after birth by the determination of urinary pregnanetriol and/or 17-ketosteroid exeretions. Whether it is of the salt-losing type cannot be so easily established. Even if the delivery occurs in an institution which has the facilities for complex chemical determinations, the diagnosis rests on the clinical acumen of the attending physician to interpret correctly the dramatic signs and symptoms. After the syndrome has been correctly identified and the patient treated, he may then be referred for long-term care. It should be remembered that the clinical presentation of adrenal crises is the same regardless of the etiology.[4] If an infant presents the clinical picture of an adrenal crisis, he should be treated, initially, with salt, desoxycorticosterone acetate (DOCA), and cortisone. The prime importance of clinical impressions is indicated by the following four cases.

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CASE REPORTS

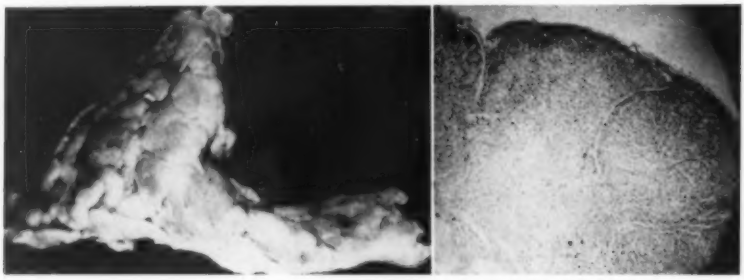
CASE 1 (Fig. 1).—

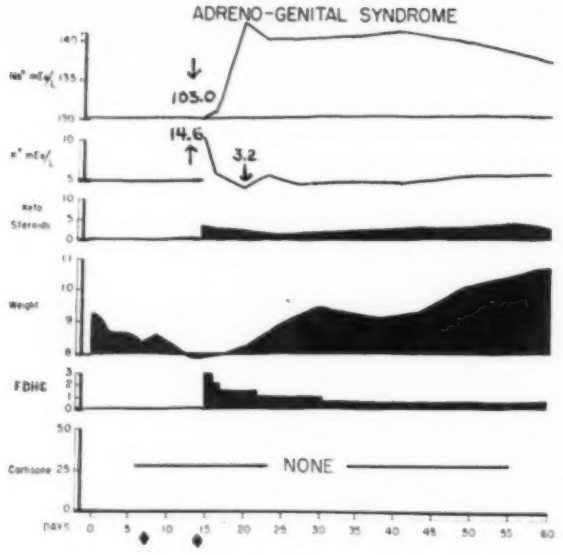
Family History.—The parents were both Caucasian of undetermined ethnic origin. The father was born in 1929 and the mother in 1930. The first child, of which little is known, died at the age of 3 days following a premature delivery. There was no family history in either lineage of congenital

malformation or hereditary diseases. Both parents have had apparent normal health.

Early Manifestations and Course.—The second child, weighing 9 pounds, 4 ounces, was born after an uneventful pregnancy and delivery on July 24, 1955. He was breast-fed. On the fourth day of life he was discharged home. On the seventh day of life he commenced vomiting. At first it was projectile and then occurred after feedings. He appeared moderately dehydrated and was hospitalized at an Air Force Base Hospital at Ruislip, England. The physicians suspected a congenital anomaly of the gastrointestinal tract, but a gastrointestinal series was normal. He was given parenteral fluids, rehydrated, and discharged home in two days. Following discharge he continued to eat poorly

A.





B.

Fig. 1.—Note the pseudoadenomatous surface of the hyperplastic adrenal. On cross section (×42) the zona glomerulosa is virtually absent and remaining zones are ill-defined. The diamonds represent periods of crisis. The initial crisis occurred on the seventh day of life, accompanied by weight loss, hyperkalemia, and hyponatremia. Note the excellent response to FDHC (fluorodihydrocortisone) and supplementary salt.

and to lose weight. Three days later he again began to vomit. At the age of 14 days he was admitted to The Great Ormond Street Hospital for Sick Children, London. At the time of admission he was described as a pale gray infant, hypothermic (95.4° F.); pulse, 110; respirations, 50 per minute; blood pressure, 75 mm. Hg systolic; weight, 8 pounds; dehydrated with a depressed fontanel. Blood chemistries on admission were as follows: serum potassium, 14.6 mEq.; sodium, 103 mEq.; chlorides, 75 mEq. The electrocardiogram demonstrated high T-waves and depressed S-T segments, indicative of a marked degree of hyperpotassemia. A diagnosis of adrenal insufficiency was made.

Progress and Treatment.—The child was under the care of Dr. Lightwood. The apparent adrenal cortical insufficiency was treated with scalp vein infusions of normal saline and with fluorodihydrocortisone (FDHC), 1 mg. at once, followed by 1 mg. of FDHC twice daily. The baby's color and vigor improved rapidly, and the following day he was given stock formula with 2 Gm. of added sodium chloride. The supplementary salt was continued daily in the feedings. The 2 mg. of FDHC proved to have too great an effect on the electrolytes, resulting in a fall in the plasma potassium to 3.2 mEq. and a rise in the sodium to 153 mEq. Therefore, the dosage had to be reduced steadily over the course of the next three weeks to a maintenance level of 0.2 mg. at 12-hour intervals. The added salt was gradually reduced, and at the age of 6 weeks it was discontinued. A 24-hour excretion of 17-ketosteroids performed on Sept. 9, 1955 (age, 5½ weeks), was 2.19 mg. The child was discharged on September 13, receiving FDHC, 0.2 mg. twice daily. The weight was 10 pounds and the serum electrolytes were normal at this time. In October, 1955, the infant and parents were transferred to the Walter Reed Army Hospital area for follow-up care. On October 23 we received a letter from Dr. Lightwood describing two infants treated with FDHC in whom hypertension developed. A subarachnoid hemorrhage developed in one of these children. On October 24 we admitted the child to Walter Reed Army Hospital for the purpose of discontinuing this medication and initiating a new regimen.

Hospitalization in Walter Reed Army Hospital.—(Oct. 24 to Nov. 23, 1955.) On admission the 3-month-old infant appeared well developed, well nourished, alert, and active. The admission weight was 13 pounds, 1 ounce. The genitalia appeared to be of normal size and configuration for a male infant. There was no apparent enlargement or increase in pigmentation. His temperature was 99.8° F.; pulse, 120; blood pressure, 100, systolic, by the flush technique. The white blood count was 21,000, with 19 per cent neutrophils, 76 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophils. Hemoglobin was 12 Gm.; hematocrit, 38. Blood chemistries were as follows: sodium, 127.5 mEq.; chlorides, 109 mEq.; potassium, 5.2 mEq. The chest film was normal; the electrocardiogram revealed peaking of the T-waves which suggested possible hyperkalemia.

Course in the Hospital.—The FDHC was discontinued on Oct. 24, 1955. Serum corticosterone was 11 μg/100 c.c. and serum hydrocortisone, 3 μg/100 c.c. on this date. (Controls: corticosterone, 7 μg/100 c.c.; hydrocortisone, 3 μg/100 c.c.) During the next four days there was a gradual but steady drop in weight and on the morning of October 28 the weight was 12 pounds, 7 ounces. On October 27, the 24-hour excretion of 17-ketosteroids was 2.7 mg. The serum sodium was 122.5 mEq., and the serum potassium, 7.6 mEq. The serum compound B, 22 μg/100 c.c.; serum compound F, 11 μg/100 c.c. On the morning of October 28 the child suddenly began to vomit. Within a short time he became

ashen, hypotensive, lethargic, and beads of cool perspiration appeared on his forehead. With these findings, a clysis of 120 c.c. of 0.9 per cent sodium chloride in water was started, and 2 mg. of DOCA plus 25 mg. of cortisone was administered intramuscularly. There was an almost immediate reversal of what had appeared to be a progressive course of deterioration. DOCA and cortisone were continued at 1 mg. daily and 6.25 mg. every six hours, respectively. During the next seven days his weight remained stable at 12 pounds, 10 to 12 ounces. On November 5, 1 Gm. of salt was added to his daily formula of 17 ounces of water, 13 ounces of evaporated milk, and 2 ounces of Karo. With the additional salt, the weight increased during the following four days to 13 pounds, 14 ounces. On this date, November 9, the DOCA was discontinued. The weight gain continued, but at a slower rate. On November 16 the supplementary salt was discontinued. He appeared to maintain his weight with cortisone alone. He was discharged on November 23, normotensive, with a weight of 14 pounds, 4 ounces; serum sodium of 145 mEq. serum K of 4.8 mEq., and a 24-hour excretion of 17-ketosteroids of 0.8 mg.

Course Following Hospitalization.—During the next three months, he was seen in the Out-Patient Clinic at two-week intervals. On November 22 the serum compound B was 10 μg/100 c.c. and the serum compound F was 8 μg/100 c.c. The cortisone dosage remained unchanged. He was not given supplementary salt or DOCA. He continued to gain weight slowly. On December 14 the serum electrolytes were essentially normal. On February 10, 1956, the mother brought the child (aged 6½ months) to the Out-Patient Clinic with the history of vomiting the previous day. The mother had added about 3 Gm. of salt to the formula of February 10, and the child retained the formula that morning. Physical examination of the child revealed him to be active and well hydrated. His color, however, seemed a little "gray." His rectal temperature was 99.6° F. There was no evidence of infection in the ears, pharynx, or chest. The mother was instructed to bring the child back if untoward signs of vomiting, diarrhea, pallor, or weight loss occurred. The child continued to eat poorly and vomited occasionally for the next day and one-half. He seemed fairly active, however, and the parents were not alarmed. On February 12, 1956, a marked gray pallor developed, and the child suddenly became unresponsive. He was dead when he arrived at the hospital 40 minutes later.

Autopsy Report.—A complete autopsy was performed. The additional information was confined to the adrenals (Fig. 1, *A*).

Gross: Both adrenals weighed a total of 15 Gm. This is about two to three times the normal weight. Both adrenals had a large but relatively normal configuration, and were a dull yellow-tan. The external surfaces were finely convoluted with deeply invaginating cortices. Multiple cut sections revealed no gross evidence of tumor.

Microscopic: Microscopic examination revealed multiple pseudoadenomatous nodules of cortical cells. The three zones of the cortex could not be defined in all areas. All of the cortical cells were uniform in appearance. The cytoplasm was typically granular. The cell nuclei were rounded and vesicular. There was no evidence of neoplasm in the microscopic sections examined.

Discussion of Case 1.—The serum steroid values for compounds F and B are noted, but since we have so few normals with which to compare them, we cannot interpret them at this time. The limiting factor in the past has been the large amount of blood needed for each determination. Currently, Dr. McLaughlin of the Walter Reed Army Institute of Research is employing a technique utilizing 2 to 2.5 c.c. of serum for determining compound B

and compound F levels. He plans to publish a statistical study after a thousand determinations.

The child died from an adrenal crisis which may or may not have been precipitated by a minor unrecognized infection. This unfortunate result emphasized to us the importance of continuing supportive DOCA and supplementary salt treatment for a salt-losing infant, even when he "seems" to be controlled with cortisone alone.

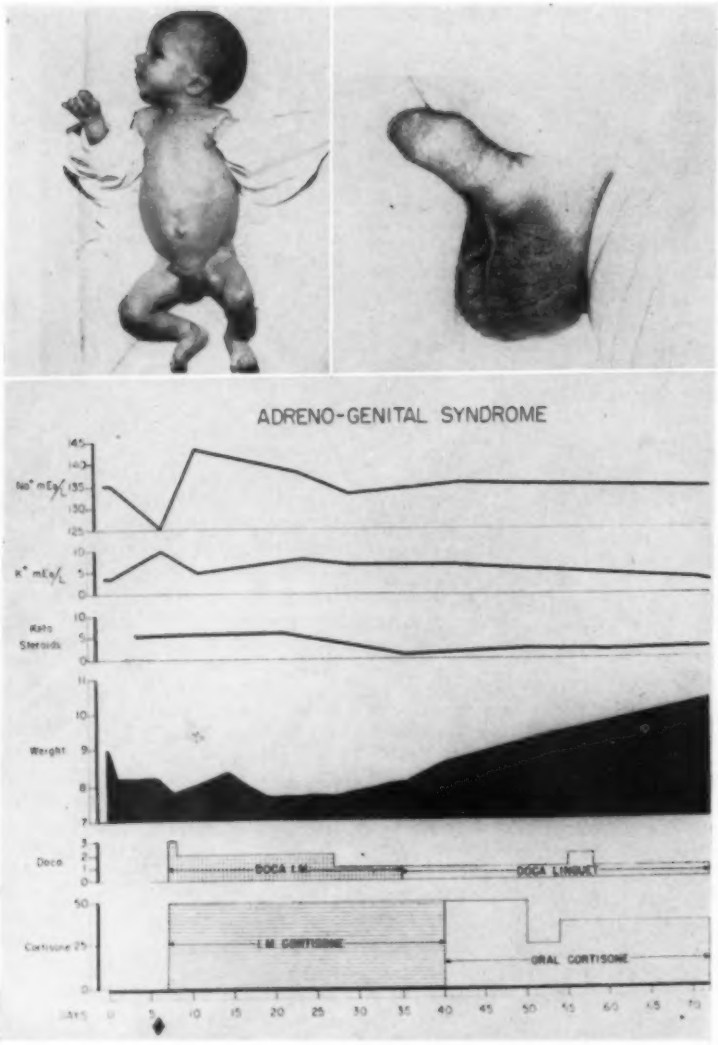
CASE 2 (Fig. 2).—

Family History.—The parents of the patient in Case 1 were repeatedly and emphatically warned that the disease their second child had was an inherited metabolic anomaly and that subsequent pregnancies might well produce children with the same disease. The mother, however, again became pregnant, and on July 24, 1956, she gave birth to a full-term, 9-pound male infant at Walter Reed Army Hospital. We had anticipated the delivery and were prepared to study the child from birth, recording the weight, blood pressure, serum sodium, serum potassium, and excretions of 17-ketosteroids at frequent intervals (Fig. 2 *B*).

Early Manifestations and Course.—The child was delivered spontaneously by the vaginal route and without complication. The infant's condition at birth was satisfactory and no resuscitation was necessary. The initial examination at birth revealed a normal-appearing male infant. Weight 9 pounds; length, 20½ inches; head circumference, 15 inches; chest circumference, 14½ inches; abdomen, 14 inches; rectal temperature, 96.4° F.; blood pressure, 80 by flush in the right arm. The penis did not seem abnormally large, and there was no noticeable hyperpigmentation. The initial laboratory studies on venous blood were as follows: serum sodium, 135 mEq.; serum potassium, 3.8 mEq.; 17-ketosteroids, 5.6 mg. excreted in the urine during the first 24 hours of life. X-ray studies, including a skeletal survey, and anteroposterior and lateral views of the chest were all within normal limits.

Course in the Hospital.—During the first six days of the child's life, he was clinically in homeostatic equilibrium. It was noted, however, that the external genitalia appeared to be slightly more pigmented each day from the second day of life. Late in the evening of the sixth day of life, the child refused his feeding and vomited once projectilely. The following morning on rounds, the child was found to be less active than usual. His color, however, was good and his blood pressure was 110, systolic, by the flush technique. His weight had dropped from a prefeeding weight taken 24 hours before, of 8 pounds, 12 ounces to a weight of 8 pounds, 4 ounces. At approximately 11:30 A.M. the child vomited again and became ashen-gray. The blood pressure dropped to 60 mm. Hg by the flush method. A sample of blood drawn from the femoral vein at this time disclosed an elevation of the serum potassium to 8.4 and a depression of the sodium to 125 mEq. The infant appeared to be having an acute adrenal crisis and was critically ill. Cortisone, 25 mg., and DOCA, 3 mg., were administered intramuscularly at once. While a cutdown was being performed, 50 c.c. of 0.9 per cent saline was forced in by syringe subcutaneously. The cutdown was completed rapidly and without incident. Over the next two hours, 50 c.c. of 5 per cent glucose in saline and 50 c.c. of ⅙ M. lactate were allowed to drip in rapidly. Within this two-hour period there was a marked clinical improvement. The gray color greatly diminished and the blood pressure increased to 90, systolic, by flush. Twelve hours after initiating therapy he had received approximately 175 c.c. of saline and a total fluid intake of 600 c.c. The ashen color had disappeared completely and the blood pressure returned to normal. Following this initial episode he was given a daily maintenance of cortisone, 50 mg.

A.



B.

Fig. 2.—Here patient is shown at 16 days of age. Note the hyperpigmentation of the scrotum and penis. This hyperpigmentation was not present at birth. The diamond represents the initial crisis on the sixth day of life. Note the prompt return of the serum electrolytes to normal following the administration of salt, DOCA, and cortisone.

intramuscularly, DOCA, 2 mg. intramuscularly, and 3 Gm. of sodium chloride added to the daily formula of 13 ounces of evaporated milk, 17 ounces of water, and 1 tablespoonful of Karo, in three divided doses. For the next two weeks, he appeared to be stable. His weight increased slowly and his blood pressure ranged from 100 to 110, systolic. Toward the end of this two-week period we had an epidemic of bronchiolitis among the ward infants. There were seven new cases within a five-day period. On Aug. 17, 1956, the patient had the characteristic symptoms of tachypnea, dyspnea with retractions, and emphysema. The blood pressure increased to 140, systolic. The child's respiratory symptoms responded to treatment with high humidity in the croupette, tetracyclines, and a diphenhydramine-propadrine expectorant. The blood pressure, however, remained elevated. On August 18 the DOCA was reduced to 1 mg. per day and the salt supplement decreased to 2 Gm. daily on the basis of the elevated pressure. Within three days the blood pressure decreased to 80 to 90, systolic, by flush. The weight remained essentially unchanged. On August 21 the serum potassium was 7.8 mEq.; serum sodium, 135 mEq. He was placed back in the croupette with intermittent oxygen and given 250 c.c. of saline by clysis. By August 25 his respiratory symptoms had disappeared. During the next 10 days his appetite improved, he gained weight, and a Cushingoid appearance developed. The DOCA was changed to Linguet administration on the 35th day of life and was administered in this manner with some technical difficulty throughout the balance of the hospitalization. On the 35th day, the serum sodium was 136 mEq.; the serum potassium, 5.3 mEq.; 17-ketosteroids, 1.3 mg. per 24 hours; weight, 9 pounds, 11 ounces; and blood pressure, 80, systolic, by flush. Since he appeared stable and was gaining weight, we decided, on the 40th day, to administer the cortisone orally in divided doses at six-hour intervals (Sept. 2, 1956). He continued to gain weight; but there was a recurrence of the hypertension which developed over the 46th, 47th, and 48th days. The blood pressure increased to 150, systolic. The hypertension decreased when the cortisone was further reduced to a daily intake of 37.5 mg. He was discharged on Oct. 2, 1956, aged 71 days, weighing 10 pounds, 4 ounces. Serum sodium was 136 mEq.; potassium, 4.3 mEq.; 17-ketosteroids, 2.27 mg. in 24 hours; and blood pressure, 100 systolic. He was discharged on a maintenance of cortisone, 12.5 mg. every eight hours, DOCA, 1 mg. daily by linguet, and 3 Gm. of supplementary salt.

Course Since Hospitalization.—Following hospitalization and initial control of the patient's disease, he was referred to Dr. F. Bartter of the National Institutes of Health for further evaluation and care. Several attempts were made to control the electrolytes with cortisone and supplementary salt alone, but they were unsuccessful. Each time the salt-regulating steroids were removed from the regimen, the least stress of infection would cause an adrenal crisis with vomiting, hypotension, hyperkalemia, and hyponatremia. Hypertension remained a problem for the first year of life. His usual pressure, when well controlled, was 130 to 140 systolic. Any attempt to stop the use of salt-retaining hormone would result in a drop in the systolic pressure and a tendency to develop a crisis easily. Therefore, our tendency was to give salt-retaining hormones to the point where a mild hypertension would occur as a safety measure. Now, at the age of 22 months, he weighs 25 pounds and has a bone age of 16 months. The current regimen is cortisone, 12.5 mg. daily by mouth, salt, 9 Gm. daily supplement, and 10 mg. of desoxycorticosterone-trimethyl-acetate, a long-acting repository preparation which is administered intramuscularly every two weeks. The parents

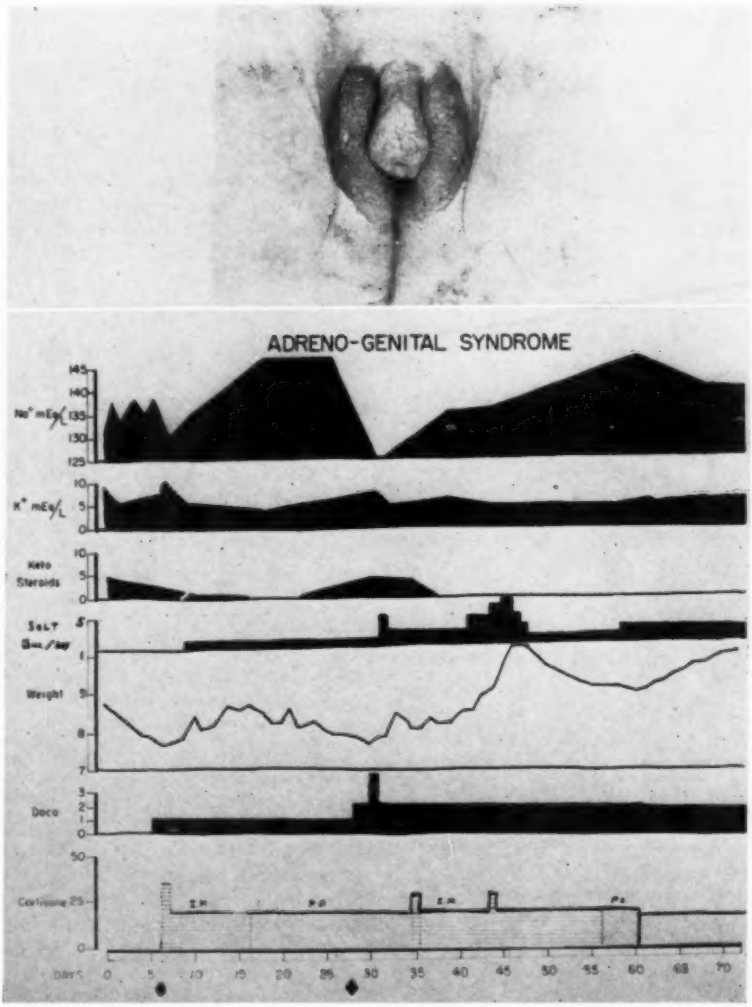
are now well versed in the signs and symptoms of a crisis and bring the child to medical attention when the early signs of crisis appear. The most reliable signs for them have been anorexia and vomiting accompanied by lethargy.

CASE 3 (Fig. 3).—

In spite of a history of having had two previous children with salt-losing adrenogenital disease, the mother again became pregnant. Following an uncomplicated pregnancy she was delivered of a full-term female infant at Walter Reed Army Hospital on Dec. 2, 1957. The first stage was 7 hours, 50 minutes; the second stage was 20 minutes, and the delivery was effected by outlet forceps. The child's cry, initially, was weak but immediate, and normal respirations were established within 30 seconds. The child was removed from the delivery room to the nursery in good condition.

Early Manifestations and Course in the Hospital (75 Days).—The initial physical examination in the nursery revealed the skin to be somewhat dark because of an increased deposition of melanin. This pigmentation was rather diffuse over the entire body but most prominent near the genitalia. The clitoris was quite large and had a raphe on the ventral surface. The vaginal orifice was in the usual position but was somewhat small. The labia were present and no testes were palpable in that location. Birth weight was 8 pounds, 12 ounces; pulse, 120 per minute and regular; blood pressure, 110 by flush. The initial laboratory data on the cord blood were as follows: hemoglobin, 15 Gm.; white blood cell count, 19,250 with 56 per cent neutrophils, 38 per cent lymphocytes, 3 per cent monocytes, and 3 per cent eosinophils; serum sodium 138 mEq.; serum potassium, 9.4 mEq. (since the cord blood was obtained by "stripping the cord," it is thought, in retrospect, that this may not have represented the true circulating serum potassium level); blood group A, Rh positive; Coombs' direct and indirect, negative; cardiolipin, negative; glucose, 126 mg./100 c.c.; total carbon dioxide, 15.2 mM; serum chlorides, 98 mEq. The child continued to do well for the first six days of life. On the seventh day, in the late evening, the child's weight was 7 pounds, 11 ounces, approximately one pound below the birth weight. At this point, she was nursing poorly; her blood pressure was 80, systolic; the skin color was slightly ashen and an adrenal crisis appeared imminent. The serum sodium was 130 mEq. and the serum potassium, 7.8 mEq. An electrocardiogram at this time was suggestive but not diagnostic of hyperkalemia. The resident on duty elected to give the child 1 mg. of DOCA, to observe the child through the night, and to repeat the serum electrolyte studies the following morning. During the following six hours, the child became less active, hypotensive, ashen, and began to vomit after her feedings. The serum potassium the following morning was 9.8 mEq. and the serum sodium was 130 mEq. Prompt treatment for the crisis was initiated: cortisone, 12.5 mg. intramuscularly at once and 6.25 mg. by mouth at six-hour intervals for the first 24 hours, and DOCA, 1 mg. intramuscularly, and 1.8 Gm. of salt by clysis and by mouth. With this regimen the child improved rapidly within a few hours. For the next nine days she did well and on the 17th day she had regained her birth weight. It is notable that the 17-ketosteroids determination decreased from 3.4 mg. per 24-hour urine excretion on the second and third days of life to 0.10 mg. on the 17th day. On the 18th day, cortisone was administered by mouth, 5 mg. every six hours. Following this change, the child stopped gaining weight although the electrolyte studies were within normal limits. On the 26th day, the 17-ketosteroid excretion was 2.8 mg. and the pregnanetriol excretion, 0.2 mg. On the 32nd day the second crisis occurred. This was preceded by

A.



B.

Fig. 3.—Note the pseudohermaphrodite clitoris and hyperpigmentation. The diamonds represent crises. Initial crisis occurred on the sixth day of life, accompanied by weight loss, hyperkalemia, and hyponatremia. Note the escape phenomena from the premature use of oral cortisone which resulted in the release of ACTH from the anterior pituitary and ended in a second crisis.

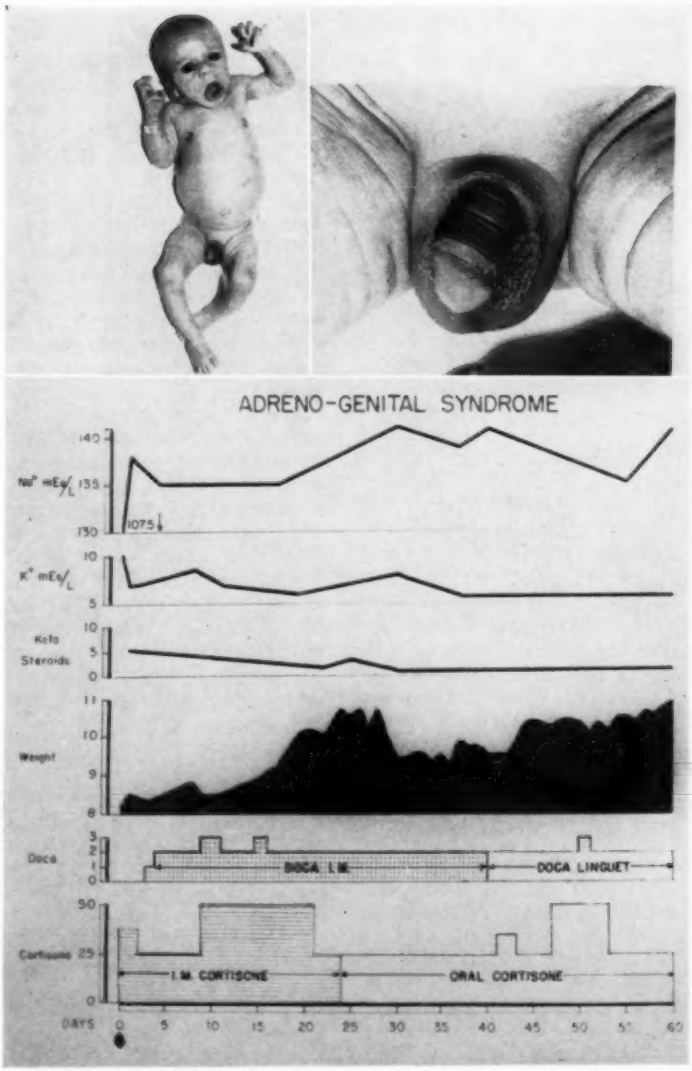
weight loss, hyperkalemia, hyponatremia, hypotension, and an elevated excretion of 17-ketosteroids and pregnanetriol. This crisis was reversed quite dramatically with the administration of 4 mg. of DOCA and a saline clysis. It was reasoned that the anterior pituitary had apparently escaped the effects of the oral cortisone sufficiently to allow the secretion of an excess of ACTH. Accordingly, the cortisone was again administered parenterally. On this regimen, the serum sodium and potassium slowly returned to normal. On the 44th day of life the infant again regained her birth weight. Also on this date she became febrile with a rectal temperature of 101.8° F. The white cell count increased to 22,000 with 89 per cent neutrophils and 11 per cent lymphocytes; hemoglobin was 7.1 Gm. and hematocrit was 27.5. A chest film disclosed a pneumonitic infiltrate in the left midlung field. This was accompanied by dyspnea, hepatomegaly, and tachycardia. The blood pressure was 110 to 120, systolic, by flush. A throat culture disclosed only alpha streptococcus and *E. coli*. Blood cultures were negative. Fearing the possibility of an early staphylococcus pneumonia, Chloromycetin was administered, 100 mg. every four hours while awaiting reports of the pharyngeal and blood cultures. The daily supplementary salt was increased in the daily formula and administered by clysis (Fig. 3, *B*). This was done in lieu of increasing the DOCA to control additional salt loss which was expected with the stress of this infection. The amount of salt added was excessive. Within two days, generalized edema developed and she gained 1 pound, 5 ounces. Because of this, the supplementary salt was decreased. This was followed by a slow diuresis over the next five days and a loss of the edema. The pneumonia responded to treatment and the hepatomegaly disappeared within one week. Following the respiratory illness and the loss of the edema associated with the salt overload, her condition again became stabilized. On the 58th day of life cortisone was again changed to oral administration at six-hour intervals. She tolerated this change without difficulty. She was discharged on Feb. 14, 1958, with a weight of 9 pounds, 14 ounces. Serum sodium was 138 mEq.; serum potassium was 6.0 mEq.; the urinary excretions of 17-ketosteroids and pregnanetriol were 0.1 and 0.0 mg., respectively. The parents were instructed to give the child 6.25 mg. of cortisone every six hours, 2 mg. of DOCA intramuscularly daily, and 3 Gm. of salt added to the daily feedings.

Course Since Leaving the Hospital.—After leaving the hospital a persistent hypertension developed, although clinically this patient was well and gaining weight at a normal rate. The DOCA was slowly decreased from 2 mg. daily to 1 mg. daily. Despite this she continued to have systolic pressures of 140 to 160 by flush. The serum potassium remained normal throughout. On April 7 (age, 4 months) she was admitted to National Institutes of Health for further study and long-term care. On admission, the DOCA was discontinued and prednisolone substituted for the cortisone. The salt dosage was maintained between 3 to 5 Gm. daily. The following week the hypertension regressed. Eleven days after discontinuing the DOCA, a crisis developed. This was controlled by parenteral salt infusions. Since this crisis she has been maintained with desoxycorticosterone-trimethyl-acetate, salt, and prednisolone. Now, at the age of 5 months, her weight is 14 pounds, 8 ounces, and her bone age is estimated at 3 months by x-ray. The hypertension has recurred but is mild (120 to 130).

CASE 4 (Fig. 4).—

Family History.—This fourth case was the fifth child of a 34-year-old Caucasian mother and a 36-year-old

A.



B.

Fig. 4.—Photograph taken on the twentieth day of life, showing macrosomia and hyperpigmentation of the external genitalia which were not present at birth. The "days" refer to days of hospitalization; the child was 12 days old and in crisis on admission. The first symptoms of crisis occurred on the seventh or eighth day of life. Again note response to DOCA, salt, and cortisone.

Caucasian father. Both of the parents were in excellent health. Two of the previous siblings, aged 8 years and 4 years, respectively, were apparently normal. Two other siblings died in infancy (the second and fourth pregnancies). The first dead sibling died at the age of 6 weeks of "kidney trouble." She was a pseudohermaphrodite. The third child died unexpectedly at the age of 6 months of "adrenal insufficiency." This child was a male. The diagnosis was not made until the condition was terminal. The fifth child was born at Walter Reed Army Hospital on June 2, 1956.

Early Manifestations and Course.—This patient was a full-term male infant, the product of an uncomplicated pregnancy and delivery. He was born on June 2, 1956, with a weight of 10 pounds, 4 ounces. The condition of the baby was excellent and no abnormal manifestations were noted during his three-day postnatal hospitalization. He did well for the first week of life. On the seventh or eighth day he began to spit up and did not seem satisfied with his breast feedings. The mother was instructed to supplement the breast feeding with an evaporated milk formula. She followed instructions, but the patient did not seem to improve. On the 12th day of life, the mother noted that he seemed lethargic, pallid, and did not suck with his usual strength. She also noted that he was still losing weight. On admission, his weight was 8 pounds, 7 ounces (a weight loss of 1 pound, 13 ounces from the birth weight); temperature, rectally, 99.8° F.; pulse, 160 per minute; blood pressure, 70, systolic, by the flush technique with a 1-inch cuff. The anterior fontanel was soft and slightly depressed. There was a slight dryness of the lips and the oral mucosa, with a slight to moderate decrease in tissue turgor. The lungs were clear to auscultation and percussion. The heart rate was regular; there were no murmurs. The abdomen was soft, without tenderness or organomegaly. The genitalia were male with a noticeable macrosomia of the penis and hyperpigmentation of the penis and scrotum.

Course in the Hospital.—The initial blood chemistry studies were: serum compound B, 8.4 μg/100 c.c.; serum compound F, 0 μg/100 c.c.; blood glucose, 103 mg./100 c.c.; CO_2, 13.5 mM; serum sodium, 107.5 mEq.; potassium, 10 mEq.; serum chlorides, 74.4 mEq. These findings helped confirm the impression received from the history and physical examination that the infant was having an adrenal crisis. An infusion of 0.9 per cent sodium chloride in water was started immediately after blood specimens were obtained for the initial chemistries. Cortisone was administered, 15 mg. by mouth at once and 6.25 mg. every six hours thereafter. Initially, the infant responded well to treatment, but we were unable to control the hyperpotassemia and hyponatremia with 25 mg. of cortisone and 2 Gm. of supplementary salt daily. Therefore, on June 17, 1956, we started the administration of 2 mg. of DOCA daily, intramuscularly. The tendency for the infant to have a hyperpotassemia persisted. On June 22 we decided to change the route of administration of the cortisone to intramuscular and the dosage to 25 mg. every 12 hours. Within two days, the serum potassium levels became normal. At the age of 4 weeks, the patient's electrolytes in the serum were essentially normal. He was still 1 pound below his birth weight, however. At this time we decreased the dosage of cortisone to 12.5 mg. intramuscularly every 12 hours. Four days following this change, which was without complication, oral administration of the cortisone was again resumed. This change was again tolerated without incident. During this transition period, the sodium chloride supplement of 2 Gm. daily was inadvertently removed from the patient's diet. It was not until he had lost 8 ounces in six hours that this error was noted and corrected. As noted in Fig. 4, *B*,

the 17-ketosteroid excretion in the urine continued to be depressed by the oral administration of the cortisone. On July 24, at the age of 7 weeks, the intramuscular administration of DOCA was changed and DOCA Linguets, 2 mg. per day, were given. The Linguets were placed under the tongue following the 6:00 A.M. feeding, and held in place with the finger until dissolved (about 10 minutes). Again, the child tolerated this change well and the blood pressure remained constant between 90 and 100 systolic by flush. Except for an upper respiratory infection, the child did well during the remainder of the hospitalization. He was discharged at the age of 2½ months, weighing 11 pounds, 2 ounces. The serum electrolytes and blood sugar values were normal. The bone age was reported as being 3½ months. The final 17-ketosteroid determination one day before his discharge was 2.1 mg. in 24 hours. The home regimen on discharge was as follows: 12.5 mg. of cortisone by mouth every 12 hours, 2 mg. of DOCA by sublingual Linguet daily, and 2 Gm. of sodium chloride added to the daily formula.

Course Following Hospitalization.—The child continued to remain clinically stable following hospitalization. He was seen in the Out-Patient Clinic at the age of 4 months and was noted at that time to be slightly hypertensive (blood pressure, 120/90) and Cushingoid. His weight was 14 pounds, 4 ounces; height, 24 inches. No episodes of true vomiting were noted during this early posthospitalization period. At the age of 4½ months he was admitted to the National Institutes of Health for further study. All treatment was discontinued for the initial study period. On the sixth day following admission an adrenal crisis suddenly developed while he was on the ward and he died despite heroic efforts by the attending staff to resuscitate him. Death was most likely due to cardiac arrest secondary to the hyperkalemia, hypovolemia, hypotension, and to the peripheral vascular collapse with shock which occurred following the withdrawal of the supportive treatment. One should be extremely cautious and acutely cognizant of a possible sudden death when DOCA and supplementary salt are withheld from the infant with a salt-losing adrenogenital syndrome.

*Autopsy Findings.**—A full autopsy was performed. The significant additional findings were confined to the adrenal gland.

Gross: The adrenal glands weighed 1.7 grams each. Multiple step sections of the adrenal glands revealed cortices which appeared intact and yellow. No tumor was present grossly.

Microscopic: The sections showed a normally convoluted adrenal cortex in which the adrenal cortical cells were not well vacuolated. The oil red-O stained sections demonstrated little or no lipoid material within the cells of the adrenal cortex. No difference was noted in the histologic structure of the left and the right adrenal glands. The adrenal medulla had not yet become fully populated with chromaffin cells. It is postulated that the adrenal atrophy was secondary to the steroid therapy.

DISCUSSION

To date, at least three forms of the adrenogenital syndrome have been described: (1) the classic form with hyperplasia of the adrenals and an associated increase in the androgenic secretions resulting in virilization; (2) type 1 associated with hypertension due to an excess production of DOCA[1]; (3) type 1 associated with moderate to severe disturbances in salt regulation resulting in hyperkalemia, hyponatremia, hypochloremia, hypovolemia, and hypotension.[2]

*Courtesy of the National Institutes of Health.

The salt-losing form of this disease is fairly common. In 25 to 30 per cent of the recognized cases of adrenogenital syndrome there is some disturbance of the electrolyte control.[3] This form of the disease first became well documented in 1939,[5, 6] but enlarged adrenals were noted in infants dying with vomiting and dehydration as early as 1905.[7] The clinical picture as noted in the preceding case reports closely resembles that seen in Addison's disease. Early attempts to define this variant of the adrenogenital syndrome more definitely were directed by the theory that this disease, like Addison's disease, was due to a deficient production of an adrenal salt-retaining hormone (aldosterone). There are three important observations, however, which suggest a different explanation.[2] (1) Infants with this disorder often require larger amounts of DOCA per square meter to regulate salt and water metabolism than do adults. (2) The administration of ACTH causes some of these infants to lose even more salt. (3) These infants actually excrete normal to elevated amounts of aldosterone in the urine.[8] The foregoing suggests that the hyperplastic adrenals may be secreting an abnormal hormone, a *salt-losing hormone*. Despite many efforts to isolate this suspected salt-losing hormone, however, it has not been conclusively identified in the serum or urine of the affected infants. Recent evidence would indicate that the basic difference between a salt-loser and a nonsalt-loser is the severity of the enzyme block in the synthesis of hydrocortisone from 17-hydroxyprogesterone.[2]

The identity of the androgenic compounds which induce the signs of virilism is still uncertain. These androgenic substances, however, are probably multiple hypersecretions of 17-hydroxyprogesterone, androstenedione, and 11-hydroxyandrostenedione.[9-11]

In 1950 Wilkins and associates[12] showed the beneficial effects of the administration of cortisone to the children with uncomplicated adrenogenital syndrome. With cortisone, the ACTH production is suppressed; this, in turn, suppresses the androgenic secretions from the adrenal. With the salt-losing form, however, cortisone is not enough. These patients also require a salt-regulating hormone (such as DOCA) and extra salt in the diet in order to control the condition.

The diagnosis may readily be anticipated in the infant who, as a female, is a pseudohermaphrodite. In the male, however, the signs of virilization may be minimal or may not be present in the neonatal period. Thus, as in the first and fourth cases, the diagnosis may not be suspected until the initial crisis. It should be apparent from our experience with the patients that all females with the adrenogenital syndrome manifested by pseudohermaphroditism, and all males suspected of this disorder, should be considered salt-losers until proved otherwise. They should be observed in the hospital for at least two weeks with attention being directed toward the weight prior to each meal and toward the oral intake and retention of feedings. Frequent blood pressure recordings should be taken, the general vigor and activity of the patient when awake should be noted; serum electrolyte studies should be done for sodium, potassium, and

chloride, and 24-hour excretions of 17-ketosteroids, pregnanetriol, and tetrahydrocortisone when available. Of these three steroid metabolites in the urine, the pregnanetriol excretion, which represents the breakdown product of 17-hydroxyprogesterone, is probably the most sensitive indicator of the enzymatic block.

Each of these four patients had his initial crisis, clinically, on the sixth or seventh day of life. It is also interesting to note that the electrolyte patterns in the two patients observed from birth were normal during this quiescent period. This would suggest an apparent intrauterine salt-regulatory mechanism which the infant loses postnatally. Others have also noted this apparently normal period in two sibling males which lasted about one week before the symptoms of weight loss, dehydration, hypotension, hyperkalemia, and hyponatremia developed.[13]

When the diagnosis of a crisis is presumed, prompt treatment is lifesaving. A salt infusion should be started at once. The salt may be given subcutaneously or interperitoneally, initially, while an attempt is being made to enter a vein for intravenous administration. Next on the priority of treatment is the administration of DOCA. DOCA, 1 to 4 mg., should be given at once either intramuscularly or intravenously, followed by a daily maintenance of 1 to 4 mg. Hydrocortisone, or cortisone, 25 to 50 mg. daily, intramuscularly, has third priority after the administration of salt and DOCA. Following the reversal of the crisis the child will usually tolerate oral fluids. At this point, salt may be added to his diet. We have found that 3 or 4 Gm. of salt seems to be adequate and is well tolerated during the early months of life. Later, the salt supplement may be increased as required. The patient in Case 2 (aged 18 months) now takes 9 Gm. of extra salt daily. One should not be in a hurry to stop the DOCA. In both of the infants who died in crises, DOCA was discontinued prematurely without substituting some other salt-retaining steroid.

Frequently, there is a temptation to discontinue the DOCA with the development of hypertension. However, before discontinuing or decreasing the dosage of DOCA, the serum potassium should be carefully noted. If the serum potassium is normal or below normal, the DOCA may be decreased slowly, but a careful watch should be made for hyperkalemia, anorexia, vomiting, weight loss, and other evidences of impending crisis. During periods of stress which occur with infections, the dosage of DOCA and cortisone should be temporarily increased. When the child is stabilized, at about 3 or 4 months of age, advice should be sought before attempting the use of long-acting DOCA-like preparations. DOCA pellets have been used successfully. DOCA pellets (two to five 125 mg. pellets) may be implanted which will last from 9 to 12 months.[4] Currently, the two surviving infants are being controlled with desoxycorticosterone-trimethyl-acetate in a repository form at two- to four-week intervals.

Cortisone is best given intramuscularly at six- to eight-hour intervals initially. By this method the amount given can be definitely established, and a depot effect can also be obtained.

By the oral method, there is greater variance in the rate and amount of absorption. This leads to the escape of the anterior pituitary, with the resultant secretion of excessive amounts of ACTH (Case 3). The cortisone may be given orally starting at about the age of 40 to 50 days, at six- to eight-hour intervals. If the tendency to escape continues, intramuscular administration may be reverted to or the oral dose may be increased.

Excessive cortisone administration may result in growth arrest or retardation. Cortisone dosage may be evaluated by noting the bone growth by x-ray and attempting to approximate the dosage between the amount needed to prevent excessive virilization and that needed to prevent excessive retardation of growth. This is indeed a delicate balance. Pregnanetriol, which is found in the urine in significant quantities only with the adrenogenital syndrome, disappears when the patient is treated with cortisone.[2] One may also be aided in regulating the cortisone dosage by giving the minimal dosage needed to maintain the 17-ketosteroids below 1 mg. excreted daily in the urine.

There has as yet been no crystallization of thought as to the duration of therapy for patients with the salt-losing type of adrenogenital syndrome. The consensus is that treatment must be measured in terms of years and perhaps for life.

SUMMARY

1. Four cases of adrenogenital syndrome, salt-losing type, are presented. They demonstrate the clinical picture of adrenal crisis in the neonatal infant.

2. The early diagnosis and treatment are of utmost importance for the survival of these infants. All females with the adrenogenital syndrome and males suspected of having adrenogenital syndrome should be observed in the hospital for the first two weeks of life in order to determine the presence or absence of electrolyte imbalance.

3. Typically, the initial crisis occurs on the seventh day of life. The crisis is characterized by a lethargic infant with a gray pallor, vomiting, weight loss, hypotension, hyperkalemia, hyponatremia, hypochloremia, and dehydration. The excretions of pregnanetriol and 17-ketosteroids in the urine are elevated.

4. In each patient, the clinical impression is much more important than the confirmatory laboratory results in making a presumptive diagnosis and initiating prompt lifesaving treatment.

5. Treatment early in life for infants with adrenal crisis includes supplementary salt administration, DOCA given intramuscularly, and cortisone given intramuscularly. Following the initial control of the patient, he should be referred for long-term care to a physician familiar with this particular problem.

6. The patients reported here took from 40 to 50 days to become stabilized on the medications after initial control.

7. Hypertension occurred with each patient who was given DOCA, but the hypertension was not severe and did not lead to any complications. When the DOCA was reduced, the hypertension disappeared.

8. Premature withdrawal of DOCA from two patients was followed by adrenal crisis and death. Therefore,

it is advisable to continue the administration of DOCA in spite of apparent electrolyte control and clinical stabilization with salt and cortisone. The maintenance of a normal weight and serum sodium level does not preclude the occurrence of a fatal hyperkalemia in these patients.

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THE CIRCULATING EOSINOPHIL LEVEL IN THE NEWBORN INFANT FOLLOWING NORMAL AND DIFFICULT LABOR

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INCREASING interest has been created recently in the study of the circulating eosinophil level in the newborn infant. Apart from its important academic value, the knowledge of the normal variations which immediately follow birth is of the greatest significance in the assessment of the adrenal cortical activity at that age. The eosinopenic response to stress has been recognized by Zappert[19] in cases of acute fulminating infections. More recently, Selye[13] included eosinopenia among the manifestations of the alarm reaction. This eosinopenic response was concluded by Hills, Forsham, and Finch[7] to be induced by the release of 11-oxycorticoids by the adrenal cortex.

The circulating blood eosinophils are derived from the bone marrow eosinophilic myelocytes. At present, little is definitely known about their function. They possess some power of phagocytosis and it is strongly suggested that they are principally concerned with the removal or detoxification of certain foreign substances.[18] Although the process of eosinophilia is described in a big group of disorders, its causation in the majority of them is by no means clear. It is believed that in many conditions it is a protective mechanism by which the organism reacts against the introduction of a foreign protein.[1] This reaction usually occurs after a latent period and is accordingly suggested to be of allergic origin.[4] In those instances when no foreign protein is incriminated it can be assumed that a protein product set free by the body, in response to a pathological process, is the immediate causative factor.

The values for circulating eosinophils in the early neonatal period have been studied by a number of workers, with rather controversial results. Lippman[9] and also Mitchell[11] reported wide fluctuations in eosinophil counts following birth. On the other hand, the results obtained by Burrell[2] and then four years later by Matheson, Rosenblum, Glazer, and Dacanay[10] agreed in demonstrating a progressive rise in circulating eosinophil counts.

The present work was accordingly intended to make a detailed study of the normal pattern of circulating eosinophils immediately following birth. It was also undertaken to investigate the possible effects of the various types of delivery on the height and stability of the eosinophil level.

PART I. METHOD AND PROCEDURE

Sixty-one infants were included in this investigation. Eosinophils were counted in a bright-line counting chamber, the following solution being used as a diluting fluid:

Eosin, aqueous 1 per cent	2 c.c.
Acetone	1 c.c.
Distilled water to	20 c.c.

From the Department of Paediatrics, University of Alexandria.

The solution had to be filtered before use and then refrigerated. With this fluid the granules in the eosinophils were the only elements to take the red stain.

Five counts were made during the first 24 hours after birth. These were started immediately on delivery and then were undertaken at ½ hour, 6 hours, 12 hours, and 24 hours. Thereafter, only one count every 24 hours was made till the fourth day. To avoid errors due to the possibility of a diurnal variation as suggested by Swanson, Bauer, and Ropes[14] and also by Tatai and Ogawa,[15] all the daily counts were performed at about midday. Counts were all made on capillary blood obtained by heel stab.

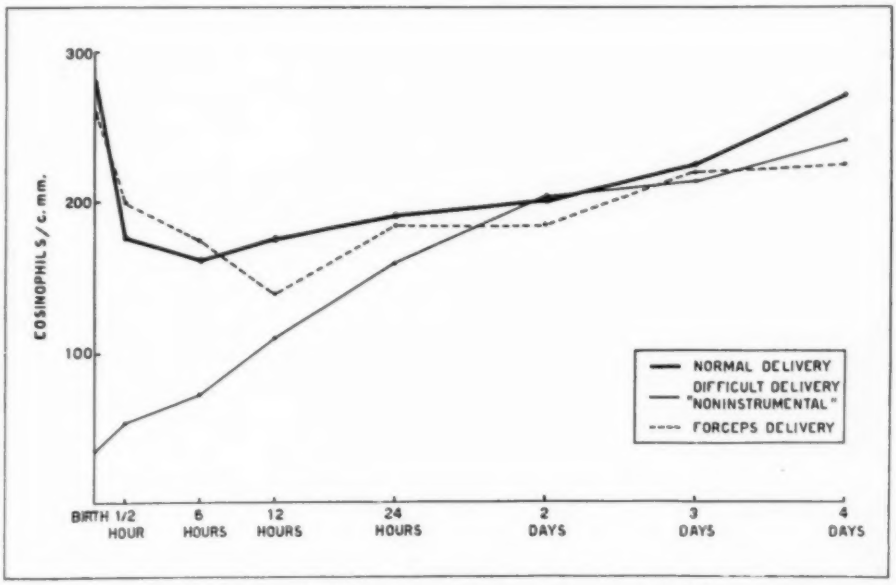

Fig. 1.—Mean eosinophil level following normal and difficult labor.

RESULTS

Group I.—Table I shows the values obtained in 22 infants belonging to this group. They were all normal healthy infants born after an absolutely normal spontaneous delivery. The duration of the second stage of labor was in all cases less than 15 minutes, and the mothers were given no anesthesia. There was no evidence of any fetal distress before delivery. The infants started respiration immediately upon birth and they showed no cyanosis or signs of birth injury.

The mean count at birth was 280 per cubic millimeter. It dropped to 178 per cubic millimeter after half an hour and to 162 per cubic millimeter after 6 hours. A gradual progressive rise was thereafter noticed and the count reached a level of 271 per cubic millimeter at the age of 4 days. (Fig. 1.)

Group II.—Twenty infants belonging to this group were investigated.

They were born after a noninstrumental labor in which the duration of the second stage was from 1 to 2 hours. Again no anesthesia was given to the mothers. Antenatal signs of fetal distress were in some cases observed. Respiratory movements in many infants started some time after birth,

TABLE I. EOSINOPHILS PER CUBIC MILLIMETER

INFANT NO.	BIRTH	½ HOUR	6 HOURS	12 HOURS	24 HOURS	2 DAYS	3 DAYS	4 DAYS
1	200	160	160	200	160	160	200	240
2	400	320	200	240	180	200	200	280
3	160	120	160	120	120	160	180	200
4	360	80	160	320	200	---	200	200
5	520	160	160	80	160	120	240	240
6	80	40	80	100	160	160	200	180
7	120	240	160	300	280	200	160	180
8	640	640	160	200	400	200	400	360
9	320	160	200	200	200	240	320	280
10	280	120	160	120	180	240	320	160
11	320	360	200	160	160	240	160	320
12	200	160	160	120	200	240	200	280
13	240	200	80	0	80	120	200	240
14	120	80	80	120	160	160	120	160
15	360	80	40	80	80	280	200	200
16	120	40	100	200	120	180	120	180
17	360	280	160	120	160	200	180	240
18	240	120	160	120	160	160	240	260
19	180	40	120	80	140	120	240	260
20	360	200	160	200	180	200	240	280
21	120	80	160	200	200	120	200	240
22	320	160	120	200	180	140	120	160
Range	80-640	40-640	40-200	0-320	80-400	120-280	120-400	160-360
Mean	280	178	162	176	191	201	229	271
Standard deviation	137	178	56	90	66	56	84	55

TABLE II. EOSINOPHILS PER CUBIC MILLIMETER

INFANT NO.	BIRTH	½ HOUR	6 HOURS	12 HOURS	24 HOURS	2 DAYS	3 DAYS	4 DAYS
1	80	120	120	160	200	200	160	280
2	0	0	40	0	120	160	180	200
3	0	0	40	40	120	280	280	320
4	40	0	0	40	80	200	140	120
5	0	40	0	40	80	120	160	160
6	80	40	120	80	160	120	240	240
7	0	80	80	200	200	200	240	240
8	80	40	--	160	120	160	180	240
9	80	160	80	80	160	240	280	280
10	0	40	160	120	220	280	120	220
11	0	40	80	80	160	180	180	240
12	80	40	120	120	120	280	240	280
13	0	40	80	80	80	120	240	120
14	80	80	120	120	120	160	240	240
15	0	40	80	120	160	160	160	180
16	120	120	160	280	240	240	200	240
17	0	40	0	40	120	180	160	200
18	40	80	80	120	120	180	200	240
19	0	40	80	80	80	120	160	200
20	0	0	0	0	160	120	-	-
Range	0-120	0-160	0-160	0-280	80-240	120-280	120-280	120-320
Mean	34	52	72	110	160	202	214	241
Standard deviation	42	43	52	74	45	64	46	55

and obvious cyanosis was an observation common to all of them. Caput succedaneum in various degrees of severity was present in many infants.

The mean eosinophil count at birth, as shown in Table II and Fig. 1, was 34 per cubic millimeter. It then increased progressively until it became 241 per cubic millimeter on the fourth day.

Group III.—Table III shows the cyanosis was present in all of them. A slight degree of birth injury was noticed in some infants.

The mean eosinophil level at birth was 260 per cubic millimeter. It showed a gradual decrease till 12 hours when it became 140 per cubic millimeter. A progressive rise then started and the level reached the height of 225 per cubic millimeter on the fourth day. (Fig. 1.)

TABLE III. EOSINOPHILS PER CUBIC MILLIMETER

INFANT NO.	BIRTH	½ HOUR	6 HOURS	12 HOURS	24 HOURS	2 DAYS	3 DAYS	4 DAYS
1	160	240	200	120	200	160	180	180
2	160	120	160	120	160	200	160	240
3	280	520	80	80	120	240	120	200
4	360	80	160	120	240	200	400	360
5	240	240	160	80	200	120	240	200
6	320	80	120	200	240	200	240	280
7	320	120	440	280	120	180	180	200
8	240	200	80	120	200	180	240	240
Range	160-360	80-520	80-440	80-280	120-240	120-240	120-400	180-360
Mean	260	200	175	140	185	185	220	225
Standard deviation	71	156	131	71	43	43	99	66

TABLE IV. EOSINOPHILS PER CUBIC MILLIMETER
(Underlining of number denotes onset of jaundice)

INFANT NO.	BIRTH	½ HOUR	6 HOURS	12 HOURS	24 HOURS	2 DAYS	3 DAYS	4 DAYS
1	260	180	160	–	180	400	320	240
2	320	280	40	120	160	440	120	200
3	320	80	120	40	400	160	200	240
4	180	200	160	80	200	160	520	200
5	40	40	0	120	80	480	40	120
6	320	80	120	200	240	640	680	640
7	0	0	40	80	160	120	180	200
8	240	400	400	200	240	200	600	360
9	180	40	120	160	400	160	200	200
10	320	400	160	40	280	160	160	240
11	600	280	160	240	180	160	400	400

values obtained in 8 infants delivered by forceps. The indications for the use of forceps in these cases were a second stage of labor of more than two hours and signs of an increassing degree of fetal distress. The anesthesia used in all cases was ethyl chloride and ether. There was some delay in the onset of respiration in most infants, and a marked degree of

Group IV.—During the course of the work, eleven infants developed physiological jaundice. Nine of them were born after a normal easy labor, and according to the previous criteria could be included in Group I, and two were cyanosed and similar to those belonging to Group II. The time of onset of jaundice was after 24 hours in three infants, at the age of 2 days

in four, and at the age of 3 days in four. In ten infants the eosinophil count on the day on which jaundice started to be clinically manifest showed a sharp rise. (Table IV and Fig. 2.) There was almost no change in the eleventh infant. Comparing these values to the mean counts obtained for similar infants belonging to Group I and Group II on corresponding days, this eosinophilic response was found to range from 140 to 340 per cent. The count remained high for only one day in seven infants, for two days in two infants, and for three days in one infant.

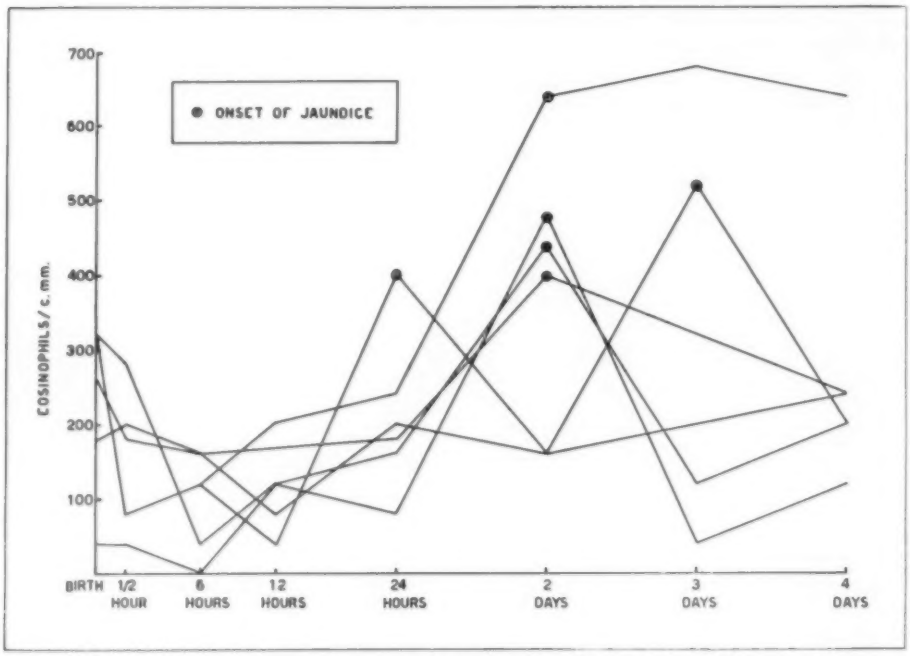

Fig. 2.—Eosinophil pattern in infants developing physiological jaundice. Graphic representation of the first six cases.

PART II. PROCEDURE

Anesthesia was thought possibly to be responsible for the preliminary high level of circulating eosinophils in infants delivered by forceps, compared to that encountered in infants born after difficult noninstrumental labor. To study this effect, a group of ten infants was investigated. These were all males, about 1 week old, and were given general anesthesia prior to circumcision. Induction was carried out by a very small dose of ethyl chloride and the anesthesia was then maintained by ether.

Eight eosinophil counts at half-hourly intervals were made. These were started one hour before induction and then regularly carried out until 2½ hours after termination. The operation in all cases was performed in the shortest time possible.

RESULTS

Table VII and Fig. 3 show the results obtained in this investigation. Two infants had physiological jaundice and showed a high original level of circulating eosinophils (400 to 560 per cubic millimeter). The level in the remaining eight ranged from 80 to 240 per cubic millimeter. Half an hour after the administration of anesthesia the eosinophil level showed an obvious rise in nine infants. A gradual drop in the majority then started and the original level was reached after 2½ hours in most cases. In the tenth infant an increase started after a preliminary drop for ½ hour. The rise attained after anesthesia was found to range from 120 to 450 per cent of the original level.

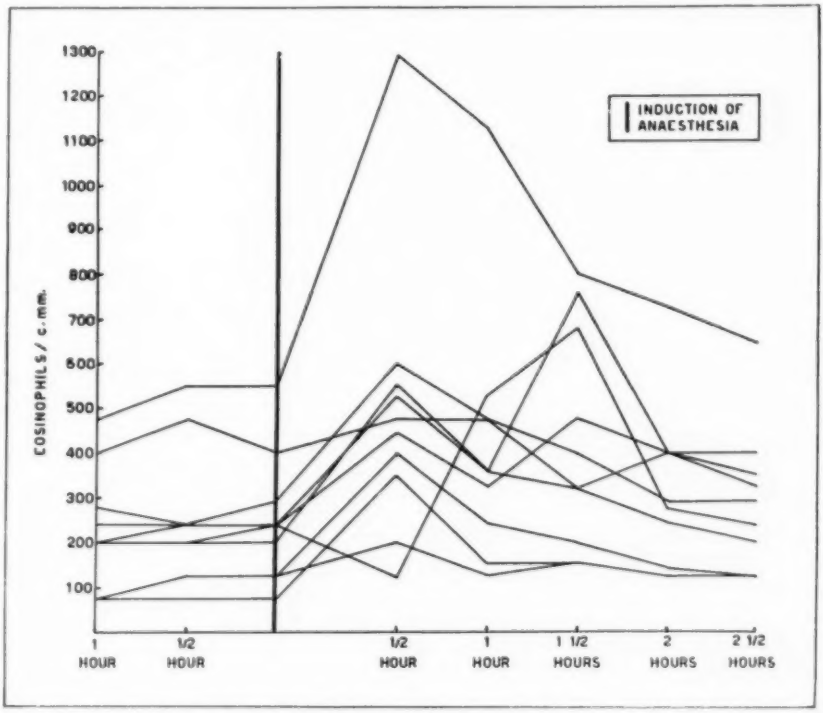

Fig. 3.—Effect of ethyl chloride and ether anesthesia on the eosinophil level.

DISCUSSION

A statistical comparison between the results obtained for Group I and Group II is shown in Table V. It is clear that at birth, after ½ hour, and after 6 hours, the difference of means is highly significant. This turns to be of slight significance after 12 hours, and of no significance at all after that.

Taking into consideration that labor is a stress to which the fetus is subjected during its passage through the birth canal, and assuming that the adrenal cortical function is normal at that age, those differences can be reasonably explained.

White and Sutton[17] obtained adequate eosinopenic responses after injecting healthy full-term infants with Adrenalin. They accordingly concluded that infants possessed a normal pituitary adrenal mechanism. Klein and Hanson[8] employed corticotrophins instead of Adrenalin in the Thorn test.[16] They reported a positive eosinopenic response in infants during the first 3 days of life. Also, Bogin, Gottfried, and Levyeky,[2] in a study on male infants of 1 to 5 days of age, reported an increase of over 20 per cent in the excretion of the total neutral 17-ketosteroids after the administration of corticotrophins.

It can be speculated, therefore, that in Group I the stress of labor was of short duration and moderate degree. This induced a mild eosinopenic response which was demonstrated for only 6 hours and was thereafter followed by recovery. In Group II when the stress of labor was very severe and of several hours' duration, the infants were born with an already very low level of circulating eosinophils. After birth, this level started to rise very gradually and recovery was complete after a period of about 12 hours. This speculation agrees with the results obtained by Farquhar[6] when he used variable doses of corticotrophins in employing the Thorn test. He found out that increasing doses of corticotrophins induced a proportionate increase in the mean eosinopenic response. After 12 hours, in both groups, when the recovery from the stress of labor was complete, the circulating eosinophil level showed a gradual progressive rise.

Contrary to expectation, the eosinophil level in infants delivered by forceps was at the onset dissimilar

TABLE V. COMPARISON OF RESULTS BETWEEN GROUP I AND GROUP II

INTERVAL	MEAN		STANDARD DEVIATION		DIFFERENCE OF MEANS	STANDARD ERROR OF DIFFERENCE	DIFFERENCE / STANDARD ERROR OF DIFFERENCE
	GROUP I	GROUP II	GROUP I	GROUP II			
Birth	280	34	137	42	246	31	7.9
½ hour	178	52	178	43	126	33	3.8
6 hours	162	72	56	52	90	17	5.2
12 hours	176	110	90	74	66	26	2.5
24 hours	191	160	66	45	31	17.5	1.7
2 days	201	202	56	64	1	20	0.05
3 days	229	214	84	46	15	21	0.7
4 days	271	241	55	55	30	17	1.7

TABLE VI. COMPARISON OF RESULTS BETWEEN GROUP II AND GROUP III

INTERVAL	MEAN		STANDARD DEVIATION		DIFFERENCE OF MEANS	STANDARD ERROR OF DIFFERENCE	DIFFERENCE / STANDARD ERROR OF DIFFERENCE
	GROUP II	GROUP III	GROUP II	GROUP III			
Birth	34	260	42	71	226	29	7.8
½ hour	52	200	43	156	148	60	2.4
6 hours	72	175	52	131	103	51	2
12 hours	110	140	74	71	30	32	0.9
24 hours	160	185	45	43	25	19	1.3
2 days	202	185	64	43	17	22	0.7
3 days	214	220	46	99	6	39	0.1
4 days	241	225	55	66	16	28	0.5

to that obtained for infants born after difficult but noninstrumental labor. Table VI shows a comparison between the results in the two groups, with an evident highly significant difference at birth and a slightly significant one after ½ hour. Anesthesia reaching the fetus through the placenta during forceps delivery was thought to be the possible causative factor, and the results shown in Table VII could easily confirm this view. It can be suggested therefore that though infants delivered by forceps are subjected to a very severe degree of stress, ethyl choride and ether reaching them while still in utero induce eosinophilia which gradually disappears once the infant is born. After 12 hours the eosinophil pattern becomes similar to that encountered in the previous groups.

As already described, physiological jaundice was found to induce eosinophilia. Eosinophilia was also said to be common in cases of icterus gravis by Parsons, Hawksley, and Gittins.[12] Farquhar,[5] and also others, observed a trend toward a higher eosinophil level on the third day of life than at any other time during the first 10 days. Although no mention was made of the presence of icterus, a mild degree of the latter could possibly have been responsible.

The mechanism of eosinophilia in these cases is by no means clear. It seems probable, however, that high bilirubin levels of the blood, though unfortunately not estimated in the present series, are among the factors concerned.

Table VII. Eosinophils per Cubic Millimeter

Case No.	Physiological Jaundice	Count before anesthesia			Count after anesthesia				
		1 hour	½ hour	Immediately	½ hour	1 hour	1½ hours	2 hours	2½ hours
1	–	200	240	240	120	520	680	280	240
2	–	280	240	240	520	360	760	400	320
3	–	200	200	240	440	320	480	400	360
4	–	240	240	280	600	480	400	280	280
5	–	200	200	200	560	360	320	240	200
6	+	400	480	400	480	480	320	400	400
7	+	480	560	560	1280	1120	800	720	640
8	–	80	120	120	200	120	160	120	120
9	–	80	80	80	360	160	160	120	120
10	–	80	120	120	400	240	200	160	120

SUMMARY

The values for circulating eosinophils in the early neonatal period were studied in 61 infants and the following results were obtained:

1. In those infants born after an easy normal spontaneous delivery the mean count at birth was 280 per cubic millimeter. It dropped to 178 per cubic millimeter after ½ hour and to 162 per cubic millimeter after 6 hours. A gradual progressive rise was thereafter noticed and the count reached a level of 271 per cubic millimeter on the fourth day.

2. Following difficult noninstrumental labor, the mean eosinophil count at birth was 34 per cubic millimeter. It then increased gradually until it became 241 per cubic millimeter on the fourth day.

3. In those infants delivered by forceps, the mean eosinophil level at birth was 260 per cubic millimeter. It showed a gradual decrease till 12

hours, when it became 140 per cubic millimeter. A progressive rise then started and the level reached the height of 225 per cubic millimeter on the fourth day.

4. Those infants who developed physiological jaundice showed a sharp eosinophilic response of 140 to 340 per cent on the day on which icterus appeared.

The effect of anesthesia on the circulating eosinophil level was studied in 10 infants. It was thought possibly to be responsible for the high level in cases delivered by forceps, as compared to those born after difficult noninstrumental labor. It was found that following ethyl chloride and ether an increase in the eosinophil level of 120 to 450 per cent lasted for about 2½ hours.

It is accordingly suggested that the stress of labor is the factor responsible for the variability of eosinophil level after birth. Physiological jaundice and anesthesia by ethyl chloride and ether are factors which induce eosinophilia.

I wish to acknowledge my deep gratitude to Dr. Ramzia Ibrahim for her invaluable help during the experimental part of the work. I am also greatly indebted to Prof. A. S. Abbassy and Prof. M. Salah for their guidance and advice, to Prof. H. Sobhy for permission to carry out the work in the Obstetric Unit, and to Dr. H. Awwad for all statistical analyses quoted in the paper.

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THE USE OF DEANOL IN THE TREATMENT OF DISORDERS OF BEHAVIOR IN CHILDREN

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DEANOL† is a new drug which accelerates mental processes, improves concentration span, and abolishes early morning "fogginess" in many individuals, according to preliminary reports.[1, 2] It also has the property of relieving lassitude and mild depression without obvious "let-down" when the drug is discontinued. Schizophrenia of long duration has shown improvement after prolonged treatment with deanol.

The amphetamines (amphetamine, d-amphetamine, methamphetamine) are the oldest and the best of the therapeutic agents available for the treatment of disorders of behavior in children,[3] but they have many side effects which limit their usefulness. Deanol appears to have advantages over the amphetamines in that there are reportedly no effects on heart rate or blood pressure, no induced "jitteriness" or anorexia, and no serious interference with sleep. One of the greatest difficulties with the use of the amphetamines in children with disorders of behavior is their control after awakening in the morning. Since the effects of even long-acting forms of amphetamine disappear in less than twenty-four hours, there is a hiatus after awakening which is filled only when the morning medication takes effect. However, the action of a single daily dose of deanol given in the morning is said to carry over to the following morning. It thus gives promise of obliterating this unsatisfactory aspect of amphetamine therapy. Because deanol was said to have a very low toxicity, to increase the attention span, and not to cause drowsiness, a clinical trial of this new drug was undertaken in children with problems of behavior.

CLINICAL MATERIAL

The patients selected for treatment were private patients of whom all but 18 were under the care of the author.* The patients, with few exceptions, had work-ups which included a history, physical (including neurological) examination, usual laboratory tests of urine and blood, an electroencephalogram, Bender Gestalt, Goodenough Draw-a-Man, psychological evaluation, and other tests when indicated. All had responded poorly to treatment with at least one other therapeutic agent, and most had responded poorly to several or had developed toxic symptoms which had caused their previous

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†Deanol (2-dimethylaminoethanol) was supplied by Riker Laboratories, Inc., as the para-acetamidobenzoate, or 'Deaner'™.

*These 18 were followed by Dr. Robert Simonds of Beverly Hills, and their histories and the results were made available by him.

medication to be discontinued. Drugs previously used included the amphetamines, chlorpromazine, Rauwolfia derivatives, pipradrol, hydroxyzine, meprobamate, captodiamine, hydantoin, methylphenidate, and barbiturates. A total of 108 nonepileptic children and 17 epilepties, all with behavior problems, were treated with deanol. There were 92 males and 33 females ranging in age from 6 months to 20 years.

All of the children in the nonepileptic group had behavioral problems severe enough to make them socially unaccepted. The greater number of them were overactive, overirritable, had a short attention span, and were doing poorly scholastically; that is, performing at a level below that expected of them based on intelligence tests. As a group they were emotionally unstable, unpredictable, and unadaptable. They belonged to the group that has been characterized by Strauss,[4] Low and Myers,[5] and Burkes[6] as being "brain injured," although this author has grave doubts concerning this terminology, and believes that many have genetic defects and many others are simply children with delayed maturation of some brain centers.

The patients were seen at regular intervals, and their responses were graded as *worse, no change, fair,* and *good* on the basis of the parents' reports, the school reports, changes in the Goodenough and the Bender Gestalt tests, and the author's observations. A "good" result was characterized by a marked decrease in abnormal behavior in all fields plus a notable improvement in scholastic achievement where this was a factor, and improvement on the Bender Gestalt and Goodenough tests. "Fair" was characterized by moderate improvement in either behavior or scholarship, or in both. Where there was doubt as to classification, the lower category was selected. Although objective evidence was sought, the final rating process was a subjective one because of the complexity of the situation.

Patients were started on either 10 or 25 mg. per day of deanol and the drug was increased at intervals of one week by an amount equal to the initial dose until improvement or hyperirritability was seen. Once a therapeutic effect appeared, the dose was kept constant at that level. Maintenance dosage ranged between 20 and 200 mg. per day, with most patients requiring about 50 mg. No other medication was taken by the nonepileptic children. In the epileptic group, deanol was taken in addition to the anticonvulsants already prescribed. No patients were evaluated who had been on the drug less than 4 weeks, except where they were made notably more irritable within that period. At the time of this writing, of the 74 evaluated nonepileptic children still receiving deanol continually, 6 have been treated more than 9 months, 21 for 6 to 9 months, 32 for 3 to 6 months, and 15 for less than 3 months.

RESULTS

The results obtained in the nonepileptic and the epileptic groups have been analyzed separately and are summarized in Tables I and II.

It may be seen from Table I that 48 per cent of the patients showed good improvement and that an additional 20 per cent showed fair improvement. In at least 10 children, the results

could have been rated as "excellent." Several children showed definite improvement in all school subjects within a single grading period (usually 6 weeks), and in many the ease and speed of reading were greatly increased. The ability to do arithmetic improved remarkably in some of the children. Important was the observation that many of the children who had obtained good or fair results with amphetamine, but who had reverted regularly in the morning before amphetamine administration to an overactive, noisy, irritable state, did not show this type of reversion when treated with deanol. In some patients who had been taken off amphetamine because of loss of weight and anorexia, a tremendous increase in appetite appeared. Five children who had had enuresis in addition to their other troubles showed complete freedom from this annoying problem while on deanol.

Table II shows the effect of the drug on the behavior and frequency of seizures in 17 epileptic patients. Of these, 10 had grand mal, 5 had mixed seizures, 1 had petit mal alone, and 1 had true psychomotor seizures. Eleven of the 17 had some improvement in their behavior, while only 3 showed improvement in seizure control, and 7 were made worse. Thus, the results in childhood epilepsy are not as good as those obtained with the amphetamines, which give greater improvement in both behavior and seizure control when used in conjunction with anticonvulsants or alone.[7, 8]

No toxic effects were observed clinically, and no adverse effect was disclosed by our routine examinations, of blood and urine (no cellular changes, albuminuria, hematuria, or increase in urinary urobilinogen). Blood pressure remained constant, and there were no changes in pulse or respiration. Three patients showed an increase in grand mal seizure activity, as might have been predicted from the primary animal studies.[2, 9] One of these, which occurred in an overactive, overirritable child with a hyperkinetic syndrome, pointed up the observations

Thirteen patients became worse. One of these developed a grand mal seizure although none had ever been observed before. The other eleven showed increased irritability and six complained of headache, particularly in the occipital region.

TABLE I. DEANOL IN THE TREATMENT OF DISORDERS OF BEHAVIOR IN 108 NONEPILEPTIC CHILDREN

WORSE		NO CHANGE		FAIR		GOOD		TOTAL	
BOYS	GIRLS	BOYS	GIRLS	BOYS	GIRLS	BOYS	GIRLS	BOYS	GIRLS
11	2	17	4	17	5	38	14	83	25
12%		20%		20%		48%		100%	

TABLE II. DEANOL IN THE TREATMENT OF 17 EPILEPTIC CHILDREN

BEHAVIOR					SEIZURES				
WORSE	NO CHANGE	FAIR	GOOD	TOTAL	WORSE	NO CHANGE	FAIR	GOOD	TOTAL
5	1	4	7	17	7	9	0	3	19*

*More patients are shown under the tabulation of seizures than of behavior since 2 patients had an increase in major seizures with a decrease in minor seizures.

of Laufer and Denhoff[10] that the convulsive threshold, as measured by the photometrazol test, is lowered in the children with this syndrome.

DISCUSSION

The results of this study indicate that deanol is a safe drug, useful in the treatment of disorders of behavior in children. For most patients of this group it appears to be superior to meprobamate, captodiamine, phenothiazine, reserpine, and other agents used. While the degree of improvement obtained with the amphetamines exceeds that obtained with deanol, the latter has the distinct advantage of eliminating the difficulties encountered early in the morning in patients taking the amphetamines. It does not cause anorexia, but rather improves the appetite in many patients, and causes no interference with sleep. The observed decrease in need for sleep in medical students[2] was not observed in these children. Of great importance to the child in school is the freedom from the drowsiness, decreased attention span, and increased reaction time found with reserpine and phenothiazine therapy. Results of testing in a few cases indicated that in some patients there was a perceptible increase in I.Q. as measured by standard tests. This indicates that so-called I.Q. tests are only a measure of functional ability at the particular time they are taken, and do not measure innate intelligence unless the individual tested is operating at maximum efficiency at the time he is tested. The decrease in overactivity, the lengthening of the attention span, and the decrease in irritability seen with its use contribute to a much better over-all social adaptation and scholastic functioning. Therefore, we find this new drug to be a most useful tool in the handling of the child with behavioral problems.

CASE HISTORIES

A. C., an 8-year-old girl, was first seen because of poor progress in school. The teacher stated that the child absorbed little. Reading and arithmetic were particularly poor in relation to the child's intelligence. She still had diurnal and nocturnal enuresis. Her coordination was poor, and if she did poorly in games or competition with other children, temper tantrums occurred. There was a question of whether she had transitory loss of consciousness and a history of seizures in the family. Physical examination showed some defect in coordination on the left as compared to the right. An electroencephalogram was reported to be severely abnormal, a sharp wave focus being present in the right temporal lobe. Paroxysmal bursts of high voltage spikes and domes resembling the classic petit mal were also present.

The patient was tried on pipradrol 2.5 mg. per day and amphetamine 17.5 mg. per day. On these scholastic improvement was noted, but the diurnal enuresis was not improved. After about two months the effects of these medications tended to wear off, and the patient's medication was changed to deanol 25 mg. per day.

This patient has now been receiving the drug for five months and is doing the best work, scholastically, that she has ever done, receiving many grades of 100 in arithmetic. A marked improvement in reading ability has occurred. The diurnal enuresis has stopped, and her eating and sleeping are much improved.

T. H., a 14-year-old boy, was seen because of "nervousness," hyperactivity, hyperirritability, failure in school in spite of normal intelligence, inattention, and marked variations in mood and performance.

There were no physical findings with the exception of some decrease in adiadokokinesis and finger-to-nose approximation. The electroencephalogram showed both diffuse and paroxysmal abnormalities. He had been tried on several drugs, including amphetamines, meprobamate, phenothiazines, and Rauwolfia derivatives, without marked improvement. He was started on deanol 50 mg. per day, and has been followed for three months. The patient is much less "nervous," his concentration span has improved, and his grades in school have improved, markedly. The variations in mood and function have stabilized markedly.

SUMMARY

Deanol, a new drug, was used in the treatment of disorders of behavior in 108 nonepileptic and 17 epileptic children. In 68 per cent of the nonepileptic group, this agent proved beneficial in that the children came to act in more socially accepted patterns and learning in school improved. In the epileptic group it was not as beneficial as amphetamine and related drugs. No toxicity or significant side effects were seen at daily doses up to 200 mg.

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OLEANDOMYCIN, A LABORATORY AND CLINICAL EVALUATION

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IN RECENT years sepsis, pneumonia, and deep abscesses due to penicillin-resistant staphylococci are being encountered by physicians with increasing frequency.[1-5] Many hospitals are instituting more stringent aseptic techniques in an effort to control the spread of this organism within their environment.[6-8] In spite of the most careful technique, these infections have continued to occur, and, for this reason, a search for effective antistaphylococcic drugs is warranted. This study was designed to evaluate the efficacy of a relatively new antibiotic, oleandomycin, in the prevention and treatment of these conditions. Serum content after various routes of administration, toxicity, and clinical effectiveness of the antibiotic were studied systematically. Cross-resistance with erythromycin was also evaluated.

MATERIAL AND METHODS

The oleandomycin phosphate* used in this study was provided by the manufacturer in crystalline form in 10 ml. vials which contained 500 mg. Dilution for intramuscular use was 125 mg. per milliliter of distilled water or normal saline. No specific dilution was used when the drug was administered intravenously. When the subcutaneous route was used, the concentration was 1 mg. per milliliter of diluent. Triacetyl oleandomycin* was utilized for oral administration.

Serum concentrations were determined after administration of 25 mg. per kilogram doses of oleandomycin. Blood samples were collected by venepuncture, allowed to clot, centrifuged, and the serum stored in a deep freeze at –5° C. The specimens were then assayed with *Micrococcus pyogenes* var. *aureus* ATCC 8668 as the test organism by the serial twofold dilution method. Patients utilized for evaluation of toxicity and clinical effectiveness were admitted to Los Angeles Children's Hospital from Nov. 1, 1956, to April 30, 1958. All patients receiving oleandomycin were included in this report for toxicity evaluation.

RESULTS

Blood Levels.—Oleandomycin phosphate, 25 mg. per kilogram, was given by a single intravenous injection, by continuous intravenous infusion over a 6-hour period, single intramuscular injection, and by hypodermoclysis. Serum samples were collected 1 to 8 hours after administration and analyzed for oleandomycin content.

As noted in Fig. 1, following a single intravenous injection, serum levels

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*Trade name of oleandomycin phosphate is Matromycin, marketed by Chas. Pfizer Laboratories, Brooklyn, N. Y.

*Triacetyl oleandomycin is marketed by J. Roerig & Company, as Tao.

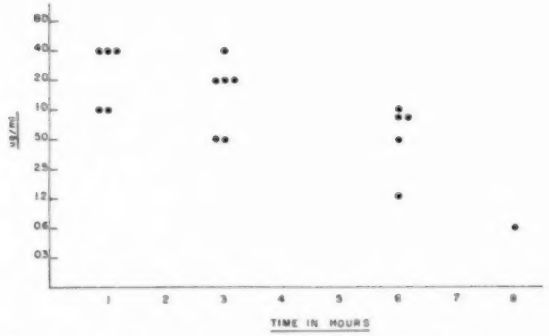

Fig. 1.—Oleandomycin serum levels after 25 mg. per kilogram given as a single intravenous dose.

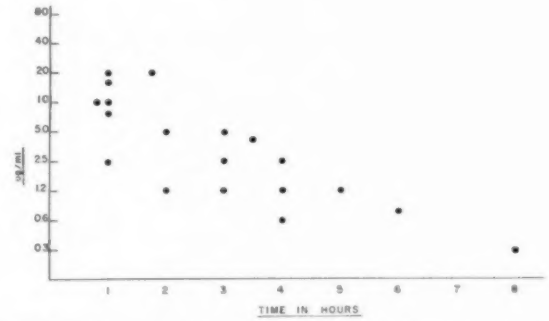

Fig. 2.—Oleandomycin serum levels after 25 mg. per kilogram given intramuscularly.

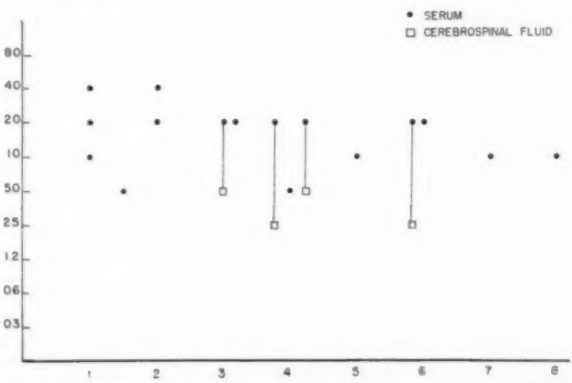

Fig. 3.—Serum and cerebrospinal fluid levels after 25 mg. per kilogram of oleandomycin phosphate given by clysis.

varied in one hour from 10 to 40 meg. per milliliter and then, after 6 hours, declined to between 1.2 and 10 meg. per milliliter. This contrasted with a consistent level of 10 to 20 meg. per milliliter during 6 hours of intravenous infusions given to four patients. Fig. 2 illustrates serum levels following single intramuscular injections. One hour after administration, the oleandomycin content ranged from 2.5 to 20 meg. per milliliter, falling rapidly to less than 1.2 meg. per milliliter at the end of 6 hours.

Toxicity.—A standard dose of oleandomycin of 100 mg. per kilogram per 24 hours was utilized for all routes of administration. Side reactions noted were local and general. Tenderness, erythema, induration, heat, and swelling at the site of injection were included under local toxicity. General toxicity consisted of any effects on the gastrointestinal tract, liver, formed elements of the blood, skin, or kidney.

Forty-five patients received continuous intravenous oleandomycin for a total of 269 patient-days. Medication

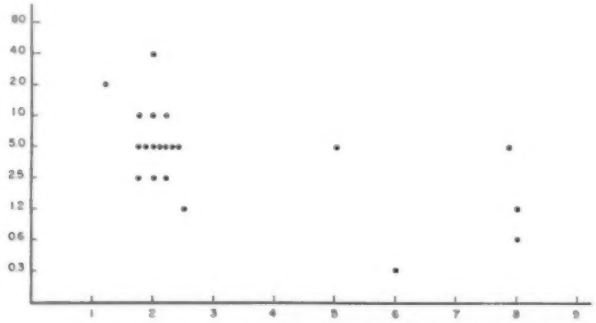

Fig. 4.—Serum levels after 25 mg. per kilogram of triacetyl oleandomycin given orally.

Fig. 3 demonstrates the serum levels achieved by hypodermoclysis. These ranged midway between the levels obtained after continuous intravenous infusion and single intravenous injection, with levels from 10 to 40 meg. per milliliter at the end of 1 hour, and declining to between 1.2 and 10 meg. per milliliter at the end of 6 hours.

As noted in Fig. 3, cerebrospinal fluid levels in the patients without meningitis were about a two-tube dilution lower than simultaneous serum levels.

Fig. 4 presents serum levels obtained 2 hours after a single oral dose of triacetyl oleandomycin. Most of the samples contained between 2.5 and 10 meg. per milliliter.

was given from 2 to 14 days, for an average of 6 days. One patient developed thrombophlebitis after 7 days' continuous administration in the same vein; however, intravenous fluid infiltrated on several occasions without any local tissue reaction.

Intramuscular administration resulted in an increased incidence of local reactions. Oleandomycin phosphate was given to 67 patients for a total of 234 patient-days. The duration of administration varied from 2 to 20 days, with an average of 5 days. The diluent used was either distilled water or normal saline. Frequently, complaints were noted of slight pain

after injection. Ten per cent developed slight to moderate tenderness and induration at the site of injection. At no time were the local reactions serious enough to necessitate discontinuing this route of administration.

Five patients were given oleandomycin phosphate by hypodermoclysis in a concentration of 1 mg. per milliliter of diluent. There were no local reactions.

Triacetyl oleandomycin was given orally every 6 hours to 82 patients for a total of 655 patient-days, in the form of either capsules or syrup. The time of administration varied from 2 to 42 days, with a median of 8.8 days. It was well tolerated, with only two patients developing nausea, vomiting, or loose stools. One patient developed proctitis and another vaginitis which was thought to be due to monilia. These cleared rapidly with antimonilial therapy and cessation of antibiotic administration.

Three patients developed jaundice after 12, 14, and 35 days of medication, respectively. Jaundice developed while patients were receiving the triacetyl form of oleandomycin. Serum bilirubins were direct 2.7 with a total of 3.3, direct 0.9 with a total of 1.2, direct 1.9 with a total of 3.0, respectively. Thymol turbidity and cephalin flocculation remained normal. The jaundice in all three instances disappeared within 3 days after medication was discontinued.

There were no skin rashes that could be attributed to the drug in any of the 136 patients to whom it was given for a total of 1,173 patient-days by all routes.

Clinical Results.—Eighty-six patients were treated with oleandomycin alone. The great majority of patients treated with oleandomycin had infections due to hemolytic *Staphylococcus aureus.* Two were found to have beta hemolytic streptococci and five pneumococci as the causative organisms. The response of the latter two organisms to oleandomycin was immediate. Eighty patients responded promptly to therapy. Table I summarizes the clinical response of the patients with a variety of infectious diseases treated with oleandomycin alone. Of particular interest was the prompt clinical response of the five children with osteomyelitis. Fifty other children received oleandomycin initially with other drugs, chiefly bacitracin and chloramphenicol. Nearly all (95 per cent) responded promptly to therapy.

TABLE I. CLINICAL EFFECTIVENESS OF OLEANDOMYCIN AS THE ONLY THERAPY IN 86 PYOGENIC INFECTIONS

	NUMBER TREATED	CURED	NOT CURED
Staphylococcic pneumonia	2	1	1
Pneumonia—other	36	32	4
Osteomyelitis	5	5	-
Abscess including adenitis and cellulitis	18	18	-
Bronchitis	3	3	-
Laryngotracheitis	5	5	-
Tonsillitis	7	7	-
Otitis media and sinusitis	8	8	-
Subacute bacterial endocarditis	1	-	1
Pyelonephritis	1	1	-
Total	86	80	6

Resistance Pattern.—Antibiotic sensitivity studies were performed on 328 staphylococcic isolates by the agar plate technique. These were performed whenever sensitivity studies were clinically indicated on staphylococcic isolates from June 11, 1957, to April 26, 1958. Nasopharyngeal cultures were

excluded from this report, thus essentially eliminating nonpathogenic organisms. Because it has been reported that oleandomycin and erythromycin have a similar range of antibacterial activity, the sensitivity of these two antibiotics was compared. Six of these isolates were found to be resistant to oleandomycin and twenty-six were resistant to erythromycin. Four of those resistant to erythromycin were found also to be resistant to oleandomycin. Table II outlines this resistance pattern.

TABLE II. COMPARISON OF RESISTANCE PATTERN OF OLEANDOMYCIN AND ERYTHROMYCIN IN 328 STAPHYLOCOCCIC CULTURES

	VERY SENSITIVE	MODERATELY SENSITIVE	RESISTANT	TOTAL
Oleandomycin	318	4	6	328
Erythromycin	295	7	26	328

DISCUSSION

The minimal inhibitory concentration of oleandomycin as reported from various laboratories ranges from 0.25 meg. to 5 meg. per milliliter in about 75 per cent of the strains of staphylococci isolated.[9, 10] The remainder would presumably be resistant to serum concentrations that could reasonably be achieved by usual methods of administration. Ninety-seven per cent of the strains isolated in our laboratory failed to grow around the disks containing 2 meg. of oleandomycin.

Serum concentrations above this can usually be found after administration by any route; however, the parenteral route is advisable when treating serious infections such as sepsis or osteomyelitis.

As noted in Table I, a variety of clinically ill patients were treated with oleandomycin alone. Response to therapy generally was prompt, with rapid subsidence of clinical symptoms. Most patients became afebrile in 24 to 48 hours, with improvement in appetite and a sense of well-being. Fig. 5 illustrates the rapid disappearance of roentgenographic findings of pneumonia after 7 days' therapy with intramuscular administration. Fig. 6 illustrates rapid healing of osteomyelitis of the fourth metatarsal with 10 days of intravenous therapy followed by 5 weeks of oral oleandomycin. Soft tissue and respiratory infections responded particularly well to therapy. Patients with sepsis, meningitis, and empyema were not treated with this drug alone, because of the high morbidity associated with such serious infections.

The question of the necessity of using such high doses as 100 mg. per kilogram per 24 hours may be raised. The dose was originally choosen for standardization of treatment, and because early reports indicated that the minimal inhibitory concentrations of oleandomycin were generally higher than those of erythromycin.[9, 10] This was not confirmed in the present study, and in view of the excellent serum concentrations demonstrated, especially by the parenteral routes, lower doses in the range of 30 to 50 mg. per kilogram per 24 hours would probably be adequate for less severe infections.

The range of antibacterial activity of this antibiotic is similar to that of erythromycin.[9] Resistance to either develops rapidly with laboratory staphylococci, and, under these conditions, the cross-resistance is nearly 100 per cent.[11, 12] This cross-resistance has been shown to be less pronounced in

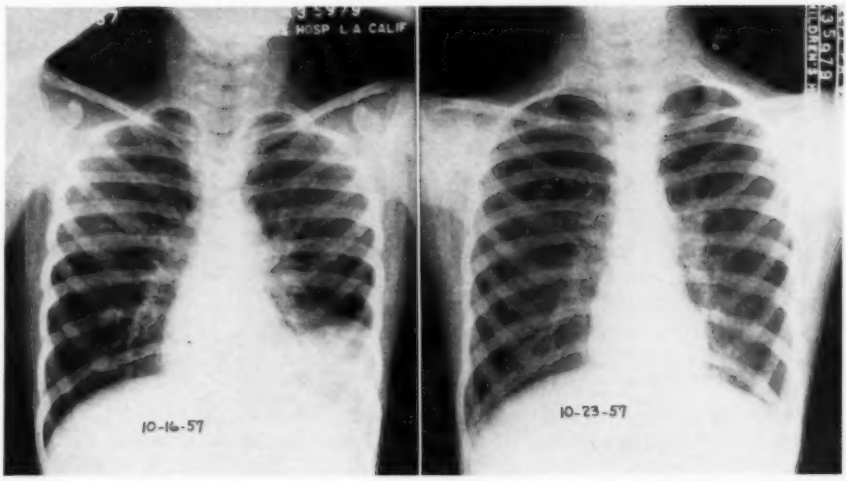

Fig. 5.—Roentgenographic change in the course of pneumonia treated with oleandomycin for 7 days.

Fig. 6.—Roentgenographic improvement in osteomyelitis of the head of the fourth metatarsal cured by oleandomycin alone.

strains freshly isolated from clinical material.[13, 14] Review of the resistance pattern from our laboratory confirms this latter observation, for only 4 of the 26 strains resistant to erythromycin were also resistant to oleandomycin.

SUMMARY

1. One hundred milligrams of oleandomycin per kilogram of body weight may be given in divided doses every 6 hours by intravenous, intramuscular, or oral routes with few minor side reactions. It can also be given by hypodermoclysis in concentration of 1 mg. per milliliter of diluent.

2. Minimal inhibitory concentrations can be achieved by any route of administration, although the highest sustained concentrations were found with continuous intravenous drip.

3. Ninety-three per cent of the pyogenic infections treated with oleandomycin alone responded promptly to therapy.

4. Jaundice was noted in three patients treated with 100 mg. per kilogram per 24 hours. It subsided promptly without residual liver damage when medication was stopped.

5. Dosage recommended for severe infections is 75 to 100 mg. per kilogram per 24 hours.

6. Ninety-seven per cent of staphylococci isolated from significant clinical sources were found to be very sensitive to oleandomycin compared to 92 per cent sensitive to erythromycin.

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GLYCOGEN STORAGE DISEASE

(Phosphorylated Intermediates in the Peripheral Blood)

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INTRODUCTION

FOLLOWING the original description of glycogen storage disease as a peculiar and specific disease entity in childhood by Wagner and Parnas[1] in 1921, numerous histories of similar cases were published in the pediatric literature.* The low fasting blood sugar and the flat epinephrine tolerance test were thought to be the result of a defect in mobilizable glycogen. However, in 1929 von Gierke[5] described the underlying pathology, and Schönheimer[6] suggested that an enzymatic defect was responsible for the excessive accumulation of glycogen in the liver, kidney, and other organs. Thannhauser and co-workers[7] were the first to call attention to a lowered alkaline phosphatase level in the liver. Further progress came from the studies of Illingworth and Cori,[8] and Cori and Cori[9] in 1952. In the first study they found by stepwise enzymatic degradation that, in one of the ten cases they studied, the liver glycogen had very short outer branches and the muscle glycogen had almost none, resembling a phosphorylase limit dextrin. In another case the liver glycogen was less branched and had longer inner and outer chains than normal glycogen, resembling amylopectin in these properties and also in solubility, x-ray diffraction pattern, and absorption spectrum of the iodine complex. In the other cases no abnormality of glycogen structure could be detected. In the second study[9] a considerable decrease of the specific glucose 6-phosphatase of the liver was demonstrated; in one fatal case in which the glycogen structure was normal, the phosphatase level was almost zero. In view of these findings the authors postulated different types of glycogen storage disease.

The present study is concerned with the tracing of phosphorylated intermediates of the glycolytic cycle in the peripheral blood of three patients following the Cori concept that in hepatic glycogen storage disease the activity of the specific liver phosphatase is either missing or is present at a very low level.

ABSTRACTS OF CASE HISTORIES

Case 1.—R. S., white male, was admitted to the hospital at the age of 7½ months with retarded development, extreme hepatomegaly, and severe acidosis. There was eruptive xanthematosis on the extensor surface of both elbows

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*Cf. the history of glycogen storage disease and the literature until 1937 in R. Wagner's,[2] and until 1947 in R. Debré's[3] monograph on this subject, also in van Creveld's review[4] in 1939.

and the posterior aspect of the neck. Fasting blood sugar values (Folin-Wu) varied from 5 to 15 mg. per cent. The urine was positive for acetone. Electrolytes were as follows: sodium 128, potassium 2.2, chlorides 92, and carbon dioxide 21 mEq. per liter. Cholesterol was 561 mg. per cent (esters 33 per cent), total lipids were 7,000 mg. per cent. No abnormal amino acids were revealed in the urine by filter paper chromatography. Recovery from acidosis was satisfactory on intravenous therapy. Glycogen content of whole blood was 15 mg. per cent (Feb. 16, 1954), of serum 19.2 mg. per cent (Feb. 23, 1954). Chromatogram on a serum tungstate filtrate revealed the presence of glucose 6-phosphate. Seliwanoff reaction in the deproteinized serum filtrate was positive.

CASE 2.—P. S., white male, was followed for five years in the Hospital for Sick Children in Toronto. He had an enormous liver extending into the pelvis. Fasting reducing value in the serum* was 8.56 mg. per 100 ml., serum glycogen content 39.6 mg. per 100 ml. There was no response of his blood sugar to epinephrine. Liver biopsy showed marked deposition of glycogen histologically. Liver biopsy slices kept for 24 hours at room temperature had essentially the same glycogen content as that found at the time of operation.

CASE 3.—D. C., 18-month-old white male, with hepatomegaly, was not markedly retarded in his general physical development. Osseus development was within normal limits. The urine was negative for acetone. Blood cholesterol was normal. Fasting sugar was 60 mg. per 100 ml. serum, completely fermentable. Glycogen content was 1 mg. per 100 ml. serum. Seliwanoff reaction in the deproteinized serum filtrate was positive. Liver biopsy was suggestive of glycogen storage disease. Direct paper chromatography on the serum tungstate filtrate showed a spot with an R_F identical with that of glucose 6-phosphate. He was re-examined at 27 months of age. He had grown well and 16 teeth had erupted. Hepatomegaly was unchanged; glucose tolerance test was diabetic in character, fasting value 108.

*Material partly clotted and slightly hemolytic.

METHODS AND PROCEDURES

The problem was studied by four different procedures: (1) preparation of the reducing sugar as a barium salt, (2) incubation of the isolated barium salt and of whole blood with phosphatases, (3) column chromatography, and (4) yeast fermentation. All of the procedures could not be applied to each of the three cases.

The reducing substances in the peripheral blood were isolated as the water-soluble barium salt from a trichloroacetic acid filtrate of whole blood by the method of Cori and Cori.[10] The water-insoluble and water-soluble fractions were precipitated together by the addition of ethanol in the first step.* The combined precipitation of both fractions is preferable, in view of the considerable amount of glycogen present in the blood in glycogen storage disease. The reductions were carried out according to the method of Somogyi.[12]

Inorganic, total and seven minutes hydrolyzable phosphorus were determined by the procedure of Fiske and Subbarow.[13] The sugar phosphates in blood and serum of Cases 1 and 3 and of normal controls were separated by ion exchange with the use of the borate complex according to Khym and Cohn.[14] The reducing power of the eluted borate fractions was determined by the Anthrone method. Filter paper chromatography followed the technique of Hanes and Isherwood.[15] The ascending method was applied, using a mixture of 80 ml. tertiary butanol, 20 ml. water, and 4 Gm. picric acid as solvent. Blood glycogen was determined by the micro modification of Pflüger's method as used in previous studies.[16]

*Cf. procedure B in Umbreit et al.,[11] p. 189.

The phosphatase preparations used in this study were recovered from horse blood leukocytes which were frozen, thawed, and homogenized, from human or rat liver homogenates, and from the intestinal tract.

Yeast fermentation was carried out on whole blood at pH between 4 and 6 with addition of 1 ml. of 0.3 M acid potassium phosphate. After adding 1 ml. of a 10 per cent aqueous suspension of washed Fleishman's baker's yeast, the suspension was allowed to stand at room temperature for 45 minutes, and deproteinized with sulfuric acid and tungstate. For the reduction of these filtrates, as well as for the unfermented blood filtrates, we used the method of Somogyi.[12]

EXPERIMENTAL DATA

1. *Barium Salt of the Reducing Substances.*—A water-soluble barium salt was prepared from a trichloracetic acid filtrate of the blood or serum of Patients 1 and 2. The barium salt precipitated from 16 ml. blood of Patient 1 was made to 35 ml. total volume. Aliquots of this were used for the subsequent procedures. Seliwanoff and Bial's reactions were negative. Reducing value, in terms of glucose, was 9.5 mg. per 100 ml. of blood. *The reducing substance was completely unfermentable by yeast.* Organic phosphorus (total minus inorganic) was 0.79 mg. per 100 ml. blood. There was a negligible amount of inorganic, and no 7 minutes' hydrolyzable phosphorus in this fraction.

In Patient 2 the barium salt was prepared from 22 ml. serum*; the precipitate was made to a total volume of 25 ml. Reducing value was 1.11 mg. per 100 ml. serum, *completely unfermentable.* Organic phosphorus was 2.5 mg. (!), inorganic phosphorus 4.01 mg. per 100 ml. serum. Seven minutes' hydrolyzable phosphorus was 0.45 mg. per 100 ml. of serum (18 per cent hydrolysis). Seliwanoff reaction was negative, Bial's reaction positive (hemolysis?). There was increase in reduction after acid hydrolysis from 1.11 mg. to 6.77 mg. per 100 ml. of blood (hydrolysis of glycogen?). Ultraviolet light absorption peak was at 248λ (inosinic acid).

A barium salt prepared from normal blood by the same procedure yielded 1 mg. organic phosphorus per 100 ml. blood. The extremely high organic phosphorus value of Case 2 may be related to the high glycogen content in the serum.

2. *Incubation of Barium Salts or Whole Blood With Phosphatases.*—The barium salt of Case 1 was incubated with a phosphatase prepared from horse blood leukocytes by freezing, thawing, and homogenizing.* From the available 0.79 mg. organic phosphorus, 0.662 mg. (84 per cent) was liberated as inorganic phosphorus during 90 minutes' incubation at pH 8.7 per 100 ml. whole blood. During the incubation period the reducing power of the barium salt rose from 9.49 to 13.4 mg. Most of the increase was due to glucose liberation from a glucose monophosphate. Its amount can be calculated from the formula: $(13.4–9.49) \times \frac{260}{180} = 5.64$ mg. Calculating from 5.64 mg. the amount of inorganic phosphorus liberated during the incubation with a phosphatase, we arrive at 0.672 mg. $(5.64 \times \frac{31}{260})$. This value agrees with the value found.

*Procedure A, Umbreit, p. 189.

*The reaction mixture was made up from 5 ml. of the barium salt and 2 ml. phosphatase preparation containing 0.6×10^9 leukocytes in borate buffer at pH 8.7 and 0.01 M final concentration magnesium sulfate (total volume 8.1 ml.).

When whole blood of Case 1 was incubated, without deproteinization, with the same leukocyte phosphatase preparation at pH 8.7, 0.825 mg. of inorganic phosphorus was liberated per 100 ml. of blood, while no phosphorus was liberated from normal blood.* The increase in reduction with the Somogyi reagent in the normal blood amounted to 5.1 per cent, in the patient's blood to 77.5 per cent.

The amount of phosphorus calculated from the increase in reduction exceeds the experimental value of 0.825 mg. by 37 per cent in this experiment. A possible explanation is that the glycogen content of whole blood (11 ml. in 18.2 ml. total reaction mixture) is to some extent responsible for the increase in reduction; some of the glycogen may break down to glucose 6-phosphate during the incubation.

The next series of experiments was carried out by incubating whole blood with a liver phosphatase (Table I).

The liver phosphatase was prepared either from human or rat livers. The former was frozen at autopsy, the latter worked up immediately. Small pieces of the organ were homogenized in ice-cold water (160 mg. fresh liver per milliliter homogenate), filtered through gauze, and the homogenate tested against glucose 6-phosphate, α-glycerophosphate, adenylic acid, and phosphoglyceric acid as substrates, at increasing pH's, before the actual experiment was carried out.

In the first two blood specimens of the patient with glycogen storage disease the liberation of inorganic phosphorus exceeded that in normal control blood by a considerable amount (Table I). Two maxima of activity were observed in the patient's blood, one at pH 5.0 and one at pH 9.0. This phenomenon was no longer reproducible one year later, when the metabolic disorder of the patient was more stabilized and the liver became smaller.

TABLE I. MILLIGRAMS INORGANIC PHOSPHORUS PER 100 ML. BLOOD LIBERATED BY A LIVER PHOSPHATASE

(Reaction mixture contained 2 ml. oxalated blood, 1 to 2 ml. homogenate prepared by homogenizing 1 Gm. fresh liver in 5 volumes ice-cold water, and 0.01 M final concentration of magnesium sulfate; pH's adjusted to 5.0 with acetate buffer, to 6.7 with citrate buffer, and to 9.0 with borate buffer, incubation time: 60 minutes)

	pH 5.0	pH 6.7	pH 9.0
Glycogen Storage Disease (Case 1):			
April 21, 1954	12.8	5.9	24.0
May 10, 1954	18.3	12.0	22.0
Nov. 24, 1954	4.0	2.2	2.5
Jan. 27, 1955	4.1	1.1	3.5
April 7, 1955	3.0	1.5	2.3
May 24, 1956	1.0	——	1.8
Normal control blood*	3.9	2.6	2.3

*These values represent averages obtained from 11 normal individuals.

The higher yields of inorganic phosphorus are not due to a difference in the rate of hydrolysis. Experiments carried out on the same patient two years later, and on normal control blood, were continued up to an incubation time of three hours. Maximum activity was demonstrated in both instances at pH 5.0 after three hours (17.2 and 16.7 per cent of hydrolyzable phosphorus respectively), at pH 6.7 after two hours (9.2 and 3.2 per cent), and at pH 9.0 after three hours (11.3 and 6.6 per cent). The intestinal phosphatase used in these experiments showed complete liberation of inorganic phosphorus at pH 9.0 with glucose 6-phosphate as substrate after

*The reaction mixture contained 11 ml. whole blood, 7 ml. leukocyte phosphatase preparation derived fom 1.06×10^9 cells in borate buffer at pH 8.7, and magnesium sulfate 0.01 M final concentration. Incubation time, 90 minutes.

three hours, with adenylic acid, α-glycerophosphate, and phosphoglyceric acid, after one hour.

Also, the phosphatase experiment on the water-soluble barium salt (84 per cent hydrolysis within 90 minutes) is an indication of the presence of hydrolyzable phosphorylated intermediates in the blood of patients with glycogen storage disease.

with 0.4 N final concentration perchloric acid, and neutralized with potassium hydroxide. It was then treated with Dowex-50-hydrogen form, and adjusted with 3 N ammonium hydroxide to pH 8.5. The equivalent of 1 ml. serum or blood was placed on a Dowex-1-chloride form column and eluted with borate buffers of varying concentration. The quantitative differences between patients and normal control, and the fractions at which the peaks occur can be seen in the table. An attempt at calculating the sugar from the organic phosphorus obtained did not agree with the observed anthrone values, since the anthrone method is not specific enough.

TABLE II. FRACTIONATION OF PHOSPHORIC ACID ESTERS IN SERUM AND WHOLE BLOOD BY ION EXCHANGE ACCORDING TO KHYM AND COHN[14]
(Results expressed in milligrams per 100 ml. blood or serum)

	PHOSPHORUS					SUGAR				
	A	B	C	D	E	A	B	C	D	E
Serum, Patient 1	4.2	20.0	18.6	23.8	24.8	16.0	88.0	96.0	120.0	84.0
Serum, Patient 3	2.9	25.3	48.0	14.7	12.0	120.0	160.0	——	406.0	107.0
Serum, normal	2.8	4.8	8.4	4.0	4.8	28.0	72.0	100.0	84.0	76.0
Whole blood, Patient 1	1.8	7.2	7.1	9.3	5.4	28.0	42.0	38.0	84.0	43.0
Whole blood, normal	3.6	5.8	3.7	8.3	4.0	104.0	37.0	24.0 (loss)	15.0	40.0

Fraction A, eluted with 0.001 N NH_4OH, contains free sugar and inorganic phosphorus.
Fraction B, eluted with 10^{-2} M borate, contains glucose 1-phosphate.
Fraction C, eluted with 10^{-4} M borate, contains glucose 6-phosphate and α-glycerophosphate.
Fraction D, eluted with 10^{-3} M borate, contains fructose 6-phosphate.
Fraction E, eluted with 0.02 M HCl, KCl, contains hexose 1,6-diphosphate.

TABLE III. IDENTIFICATION OF ELUTED PHOSPHORIC ACID ESTERS BY PAPER CHROMATOGRAPHY
(Spotted 0.1 to 0.3γ material derived from the borate fractions A through E)*

PATIENT NO.	MATERIAL	GLUCOSE 1-PHOSPHATE	GLUCOSE 6-PHOSPHATE	FRUCTOSE 6-PHOSPHATE	HEXOSE 1, 6-DIPHOSPHATE	α-GLYCEROPHOSPHATE†
1	Whole blood	+	+	0	+	+
1	Serum	+	0	+	+	–
3	Serum	+	0	0	+	–
Normal	Whole blood	+	+	0	+	0
Normal	Serum	+	0	0	+	0

*These amounts required 24 hours for development but eliminated the "ghost spots" observed when larger amounts were used.
†A known quantity of α-glycerophosphate was put on an ion exchange column and eluted with 10^{-4} M borate solution.
+ Present; 0 absent; – not done.

3. *Column Chromatography.*—Further experimental proof for a higher content of phosphorylated intermediates in glycogen storage disease serum or whole blood could be obtained by phosphorus determinations of the different borate fractions using ion exchange according to Khym and Cohn[14] (Table II).

The material was first deproteinized

In all fractions the amount of organic phosphorus eluted was higher in glycogen storage disease than in the

normal control.* The results obtained by the anthrone method are less informative.

Chromatographic studies were carried out for identification of the phosphorylated intermediates of glycogen metabolism. In preliminary experiments on the water-soluble barium salt of Case 1, "trailing," "ghost spots," and "lagging shadows" were disturbing factors in comparing the R_F values with those of the standards. Direct chromatography on tungstate filtrates of whole blood and serum were, therefore, carried out on Cases 1 and 3, using the method of Hanes and Isherwood.[15] Glucose 6- and fructose 6-phosphate were seen in specimens both unfermented and fermented by yeast. Ribose 5-phosphate and hexose 1,6-diphosphate were absent. The Seliwanoff reaction on serum filtrates was positive. Glucose 6-phosphate was also identified in normal serum, while the presence of fructose 6-phosphate was questionable. Therefore, the sugar phosphates separated by ion exchange with the use of the borate complexes according to Khym and Cohn[14] were studied by filter paper chromatography according to Hanes and Isherwood.[15] The results can be seen in Table III. In all chromatograms of the patients, unidentified organic phosphorus-containing spots were visualized. Normal blood contains the same intermediates except for fructose 6-phosphate, which was present only in the serum of Case 1, and for α-glycerophosphate present only in whole blood of the same patient.

*Due to the presence of some organic phosphorus eluted from a blank column, the sum totals of the organic phosphorus values obtained exceed those directly determined in the sera. However, the values in glycogen storage disease are still considerably above the normal values.

4. *Yeast Fermentation.*—Studies with yeast cell suspensions on the fermentability of the reducing substances in blood filtrates were unsatisfactory since the ***absolute*** values of the unfermentable remainder in glycogen storage disease blood is within the same order of magnitude as in normal blood. In normal control blood specimens 20 to 25 per cent of the total reducing substances is unfermentable. In glycogen storage disease blood, with low total reduction, 100 per cent unfermentability might be equivalent to 20 to 25 per cent in the normal.

DISCUSSION

The experimental results of this study contribute to the understanding of the chemical pathology of the enzymatic defect characteristic of glycogen storage disease. The findings of Cori and Cori[9] suggested that there are phosphorylated intermediates of the glycolytic cycle in the peripheral blood. Yeast fermentation is not an adequate procedure to demonstrate their presence. The unfermentable remainder in normal blood is within the same order of magnitude as in glycogen storage disease, where total reduction is at a low level. Better evidence for an increase of phosphorylated intermediates in the peripheral blood is furnished by the unfermentability of the barium salt of the reducing sugar and the liberation of considerable amounts of inorganic phosphorus in blood specimens incubated with various phosphatases. There is some liberation in normal blood; however, the amount of phosphorus in glycogen storage disease considerably exceeds that in normal blood, with one peak at pH 8.7 and another at pH 5.0. This indicates that glucose 6-phosphate cannot be the only substrate with phosphorus in organic linkage; in this case, maximal activity

would be demonstrable at pH 6.8. We are dealing with a mixture of different substrates.* The positive Seliwanoff reaction in the serum is most likely due to the presence of fructose 6-phosphate formed from glucose 6-phosphate by the activity of a phosphohexoseisomerase, or of fructose 1,6-diphosphate. Since the equilibrium between glucose 6- and fructose 6-phosphate is at approximately 70:30, a positive Seliwanoff reaction is only to be expected where amounts of glucose 6-phosphate larger than those in normal blood are available. In the barium salt the reaction was negative, because the concentration of the reducing substance is too low. Usually not more than 30 per cent of it can be recovered from blood by the procedure of fractionation. The increase of the reducing power of the water-soluble barium salt as well as of whole blood, following incubation with phosphatases, is also consistent with the idea that some of the phosphorylated intermediates in the peripheral blood are sugar phosphates.

One may speculate that some of the increase in reduction might be the result of glycogenolysis and the formation of glucose 6-phosphate in the crude phosphatase preparations which carry some glycogen. However, it was shown in a control experiment on the phosphatase prepared from leukocytes without addition of the barium salt that the reduction after the incubation period is negligible.†

The reducing sugar was isolated in two cases as a water-soluble barium salt. Although the relationship between reducing power and organic phosphorus does not reveal the expected ratio for a sugar monophosphate, the unfermentability by yeast and the liberation of inorganic phosphorus by a phosphatase can be considered satisfactory evidence for the presence of some phosphorylated intermediates in the peripheral blood.

The final evidence for the presence of specific phosphorylated intermediates in the serum of glycogen storage disease patients was furnished by column chromatography. Direct paper chromatography reveals intermediates of the same R_F found in normal control blood. Quantitative differences are obtainable only by column chromatography. Patient 3 illustrates this best since most of the ordinary laboratory findings were ambiguous in this mild case, except for those on column chromatography.

The experimental results of this study are consistent with Cori and Cori's[9] interpretation of one type of glycogen storage disease as a defect of liver phosphatase. The presence of reducing phosphorylated intermediates in the blood explains some of the peculiar features of this disease. The low, in some cases even missing, reducing value of the blood is not only the result of the diminished glucose content, but also of the presence of sugar phosphates of a reducing power lower than that of glucose. In contrast to glucose, the sugar phosphates are unable to penetrate the cell membrane; this inability may be responsible for the retarded physical development of the carriers of the defect. They are in a precarious metabolic situation and

*From phosphopyruvic acid, phosphocreatine, ribose 5-phosphate, and adenylic acid, for instance, inorganic phosphorus is split off at pH 8.7.

†In previous studies, Wagner and Reinstein[11] found that during phosphorylating glycogenolysis in leukocytes an accumulation of glucose 6-phosphate is demonstrable only on cell material dialyzed against distilled water and with the addition of adenylic acid. Also, a pH of 8.7 is not favorable for this reaction.

starve amid plenty. After ingestion of glucose the metabolic situation is improved only for a short time. The newly formed glucose 6-phosphate accumulates again and is partially reconverted into glycogen, since the over-all equilibria favor glycogen deposition. In this way a vicious circle is established. A complete defect would be incompatible with life. Cori and Cori[9] found glucose 6-phosphatase practically absent in the liver in two fatal cases; in the milder cases some of the glucose 6-phosphate still serves as a source of blood sugar formed from carbohydrates. Also, sugar can be formed from noncarbohydrate sources, such as amino acids; in our first study on glycogen storage disease[1] we were able to demonstrate a prompt rise of blood sugar following the ingestion of various amino acids.

Other metabolic anomalies in glycogen storage disease should be mentioned briefly. The hyperlipemia, hypercholesterolemia, and eruptive xanthomatosis may be interpreted in analogy to that occasionally observed in severe diabetes mellitus. There are cases reported with an abnormal amino acid pattern[18] in the urine. In the water-soluble barium salt of the trichloroacetic acid serum filtrate of Case 2, the peak of ultraviolet light absorption was found at 248; this is characteristic of inosinic acid. In a fraction similarly prepared from normal blood the peak was at 255 (purine absorption). The significance and the specificity of this finding should be clarified by further studies. In analogy to other syndromes with multiple congenital anomalies, linkage of one enzymatic defect with other metabolic anomalies is to be expected.

SUMMARY

The presence in the peripheral blood of phosphorylated intermediates of the glycolytic cycle has been studied in glycogen storage disease. Their amount considerably exceeds that in normal blood. Different procedures were applied to demonstrate the presence of the sugar phosphates.

The reducing substance in the blood has been prepared as a water-soluble barium salt characterized by its high organic phosphorus and its unfermentability by yeast. This salt as well as whole blood were incubated with various phosphatases; phosphorus could be liberated from its organic linkage in amounts considerably exceeding those in normal blood. An increase of the reducing power of the isolated barium salt as well as of whole blood, following incubation with phosphatases, is consistent with the idea that some of the phosphorylated intermediates are sugar phosphates.

Further proof was obtained by column chromatography. The organic phosphorus in the individual borate fractions was found to be above that in the analogous fractions prepared from normal blood. Each borate fraction was studied by filter paper chromatography; the phosphorylated intermediates were identified as glucose 1-phosphate, glucose 6-phosphate, fructose 6-phosphate, hexose 1, 6-diphosphate, and α-glycerophosphate. Normal blood contains the same intermediates except for fructose 6-phosphate which was found only in the serum of one of the patients, and for α-glycerophosphate present only in whole blood of the same patient. The Seliwanoff reaction was frequently positive in deproteinized serum filtrates of patients with glycogen storage disease.

The experimental results of this study support Cori and Cori's[9] interpretation of one type of glycogen storage disease as a congenital defect of the specific liver phosphatase. The low reducing value of the blood in this disease is not only the result of the diminished glucose content but also of the presence of sugar phosphates of a reducing power lower than that of glucose.

We are greatly indebted to Dr. A. L. Chute (Hospital for Sick Children, Toronto) for sending us the blood specimen of Case 2, to Dr. H. Shwachman (Children's Medical Center, Boston) for providing the material of Case 3, and to Ann Yourke for carrying out some of the chemical procedures.

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THE ROLE OF CANDIDA ALBICANS IN THE COMMON SKIN DISORDERS OF INFANCY AND EARLY CHILDHOOD

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A GREAT deal of interest has recently become manifest in the problem of Candida infections.[1, 2] This interest has undoubtedly been stimulated by the increasing number of case reports on generalized Candida infections which have appeared in the literature and also by the fact that this rise in incidence has appeared to be coincidental with the widespread use of antibiotics.[3-9] In addition to the interest in generalized infections, more attention has been paid by pediatricians to the role of Candida in the skin disorders of infancy.[10-13] While a specific clinical picture of Candida of the skin does occur, it is perhaps not too well appreciated that the organism may be recovered in a variety of common skin disorders.[14, 15]

Our interest was initially aroused in this problem several years ago when we observed an infant with an extensive infection of the skin. The lesions yielded Candida on smear and Sabouraud's medium and responded promptly to 1 per cent aqueous solution of gentian violet. As a result of this experience, we routinely made smears and cultures on infants with moderately severe skin lesions, irrespective of the clinical diagnosis. Over a period of two years we attempted to recover the organisms in 296 skin rashes of varying types and were successful in 90 instances (an incidence of 30.7 per cent). While the great majority of cases studied were diaper rashes, we also included cases of miliaria, seborrheic dermatitis, intertrigo, and eczema, as well as a few cases of specific moniliasis of the skin. These random observations, however, raised more questions than were answered. In a number of instances when we felt confident we would recover the organism, we were unsuccessful; whereas, conversely, on occasion when least expected, they were readily demonstrated. Moreover, despite our expectations, skin lesions occurring concomitantly with antibiotic therapy did not seem to yield the organism with any degree of consistency. The exact role of Candida in skin disorders of infancy seemed obscure and, we felt, justified a more systemized series of observations.

CLINICAL MATERIAL AND LABORATORY METHODS

Clinical Material.—Infants and children in residence at the New York Foundling Hospital, and infants, including those newborn and premature, at St. Vincent's Hospital, New York City, were the source of the clinical material utilized in this study.

The largest group of cases were those observed at the Foundling Hospital. This institution, with a capacity of 285 cribs and

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bassinets, is chiefly devoted to the care of the dependent, abandoned and neglected infant; about 40 per cent of the infants are under 1 year of age. One floor (St. Ann's 2), with a capacity of 30 bassinets, was especially useful for it houses newborn infants transferred from obstetrical services throughout the city for social disposition—in most instances, adoption. These infants are generally 6 to 10 days of age on admission and their average stay is 5 weeks, with a range of from 10 days to 3 months. The average length of stay in the remainder of the institution is 3 months. Newborn infants at St. Vincent's Hospital remain in the obstetrical nurseries for 6 days and are then discharged with their mothers. Their supervision is the responsibility of the Pediatric Division. The infants in the thirty-cubicle Premature Unit are composed of the premature infants born at St. Vincent's Hospital and those born at other hospitals. The latter are transferred to St. Vincent's by the Premature Transport Service of the New York City Health Department. The former average 19.8 days of hospital stay and the latter 34.5 days.[16] A few infants admitted for various diseases to the Pediatric Division at St. Vincent's Hospital were also included in the study.

Laboratory Methods.—The presence of Candida was determined by both smear and culture technique, separate sterile swabs being used for each test. Smears were treated with 10 per cent carbolfuchsin aqueous and declared positive when blastospores were observed.

For most culture purposes, Nickerson's medium was employed, although occasionally Sabouraud's medium was utilized. Nickerson's medium was found to be practical and convenient since the dark-brown to black colonies stand out very well against the white background of the media.[17] All cultures were incubated at 37° C. for at least 7 days before being declared negative. Isolates recovered were forwarded by mail to the Research Division of Johnson & Johnson, New Brunswick, New Jersey, where sugar fermentation and morphology tests were performed by F. Herbert Grutter, Ph.D., research microbiologist, and Harold E. Swartz, research mycologist. These workers utilized a sugar fermentation reaction for the differential identification of the majority of isolates, although later this method was discarded in favor of an observation of chlamydospore formation.[17, 18] An isolate which produced acid and gas reaction on dextrose and maltose, acid on sucrose, and no change on lactose was reported as *Candida albicans*. The method using chlamydospore formation as the criterion for *Candida albicans* was adopted because of the rapidity and simplicity of the test, and because it is apparently more reliable in making identification. Isolates showing chlamydospore microscopically were reported as *Candida albicans*. Negative isolates were reinoculated for two successive times into chlamydospore agar, and if negative results were still obtained, these isolates were reported as Candida species.

PLAN OF STUDY

Test Cases.—In order to facilitate the compilation of data, individual forms, apart from the regular hospital charts, were maintained by the observer. On these were recorded age, sex, color, dates of the onset of rashes, specific diagnosis, if any, daily clinical observations on the progress of the rashes, treatment, and mycology. All cases were observed for thrush during the course of observation, and specific past histories of thrush were recorded. Special note was made of antibiotic therapy with the dates of administration. Cases that developed rashes concomitantly with antibiotic therapy were investigated for the presence of Candida. Included in this group were infants who developed rashes within 5 days after antibiotic therapy had been discontinued. A further study of cases was made of those who developed rashes in the course of bouts of gastroenteritis. It was felt that both antibiotic therapy and gastroenteritis might predispose toward the recovery

of Candida. In order to avoid selection and bias, all infants who were admitted to the Foundling Hospital with rashes or who developed rashes during their stay were incorporated in the study. Smears and cultures were obtained separately with individual sterile cotton swabs rubbed firmly and briskly back and forth several times at the point of maximal dermatologic pathology. These were obtained before treatment was instituted, during the course of treatment if the rash was recalcitrant to treatment, and after the rash had cleared. Routine skin care of the infants consisted of soap and water bathing and cleansing and the use of a nonmedicated baby powder applied to the diaper area after each change.

Of all the skin disorders of infancy, it is well known that, numerically, diaper rashes far exceed all other types of rashes observed. Moreover, the clinical classification of diaper rashes is subject to many errors of interpretation. The intensity of erythema may vary sharply from one observer to the other. Pigmentation of the skin is another source of bias or error in recording. For these reasons, and in order to manage our data statistically, we adopted the following classification for diaper rashes:

Mild diaper rash	— Erythema of the buttocks.
Moderately severe diaper rash	— Erythema of the buttocks and either erythema of the vulva, scrotum, thighs, or abdomen.
Severe diaper rash	— Erythema of any area covered by the diaper associated with excoriation.

Although we were primarily interested in the recovery of Candida of the skin, a number of cases were followed with additional smears and cultures from the mouth and rectum.

Controls.—Infants and children who had no skin lesions were utilized as controls. Smears and cultures were separately obtained from these patients with the usual sterile cotton swabs. The swab was rubbed firmly and briskly down both groins and then in a circular arc about the buttocks 1 or 2 inches away from the anal region. As the work on the controls progressed, frequent age checks were made so that a comparable number of controls and test cases by age were obtained.

A small series of newborn infants and their mothers (49) were also studied. In these instances, a vaginal culture was obtained from the mother at delivery and on the fifth day post partum. Mouth, skin, and rectal cultures were obtained from the infants on the first day of life and on the third and sixth days. The skin cultures on the first day of life actually represented vernix, since we purposely obtained these cultures before the vernix was removed. No prophylactic measures for thrush were taken on these infants.

It was our plan to institute therapy immediately after initial smears and cultures of the skin were obtained. The compelling reason for this was that we did not feel justified in deferring therapy while awaiting the reports on mycology, which sometimes required several days. Our previous experience had indicated, however, that a specific antifungal agent would not be needed in every instance and that we would

therefore require an agent with a broad therapeutic base, i.e., antifungal, antibacterial, and one with a nonspecific healing potential.

This problem was presented to the Research Division of Johnson & Johnson who had been investigating the anti-infective activity of an acridine dye* in various ointment bases, which appeared to be of considerable promise on the basis of both in vitro and in vivo activity. This material was found to possess excellent bactericidal and bacteriostatic activity upon a wide variety of organisms. It had previously undergone preliminary clinical trial under the name Acrizane, during which it was found that in effective concentration it does not injure tissue or prevent healing.[19, 20] Since the drug appeared to offer promise, an ointment containing 0.5 per cent of the active material† was made available at our request. A comparative study of therapeutic agents was not attempted at this time since we were more interested in the relative ability of the drug to control fungal dermatitis of the skin as against dermatitis of nonspecific origin.

We used the following therapeutic index throughout the study:

Excellent	= Rash cleared within 5 days.
Good	= Rash cleared within 7 days.
Fair	= Rash cleared within 10 days.
Failure	= Rash intensified under treatment, requiring a change of therapy before 10 days, or failed to clear in 10 days.

RESULTS

This study was continued over a 2-year period, during which time we had under observation a total population of 1,447 infants. The average hospital stay was 3 months.

TABLE I. INCIDENCE OF CANDIDA RECOVERED ON THE SKIN

	TOTAL	POSITIVE	NEGATIVE	PER CENT POSITIVE
Controls	234	24	210	10.2
Diaper rashes	361	132	229	36.5
Mild	92	25	67	27
Moderate	209	81	128	38.7
Severe	60	26	34	43.3
Miscellaneous diagnoses	113	49	64	43.3
Totals	708	205	503	28.9

Table I demonstrates the frequency with which Candida was isolated from the skin. Diaper rashes were by far the most frequent condition observed, with an incidence of 24.9 per cent of the total population. This figure, incidentally, coincides well with other unpublished but long-term observations we have made in the past. It is a fairly constant percentage for our type of case material. *The data recorded are a reflection of recovery by culture media, not by smear.* (At the start of the study, as smears and cultures from the skin were obtained, it became apparent after a 6-month period that, in so far as skin mycology was concerned, the cultures were more

*9-p-hexyloxyphenyl-10-methylacridinium chloride.

†The term "phenacridane" has been adopted as the generic designation for 9-p-hexyloxyphenyl-10-methylacridinium chloride. This material is now being prepared for marketing by Johnson & Johnson under the registered name Micridium Phenacridane Cream.

reliable. For example, in 70 instances smears and cultures were studied with the following results: 56 cases yielded negative smears and positive cultures, 7 cases yielded positive smears and negative cultures, and 17 cases were positive on smear and culture. Accordingly, we tended to rely more on cultures and continued to use smears mostly for follow-up of the cases.)

TABLE II. INCIDENCE OF POSITIVE SKIN RASHES BY SEX AND COLOR

	NUMBER	PER CENT POSITIVE
White male	189	38
White female	165	40.6
Nonwhite male	69	31.8
Nonwhite female	51	39
Totals	474	38.1

ditions had an identical yield of 43.3 per cent. Cases with diaper rashes proved positive for Candida, three times more frequently than the controls (Table III). Included in the diaper rashes were 13 cases which met the clinical criteria for cutaneous candidiasis.[1, 2, 15]

Sex and color had no apparent effect on the recovery of the organism (Table II). Age does, however, play an important role (Table III). While it is true that the frequency of diaper rashes is inversely proportional to age, infants under 1 month proved positive for Candida in 44.9 per cent of cases studied; whereas, in the next 2 months of age, despite almost the same incidence of diaper rash, only 29 per cent

TABLE III. RECOVERY OF CANDIDA IN DIAPER RASHES AND CONTROLS BY AGE GROUPS

	RASHES			CONTROLS		
AGES	TOTAL	NUMBER POSITIVE	PER CENT POSITIVE	TOTAL	NUMBER POSITIVE	PER CENT POSITIVE
0-1 month	136	61	44.9	81	8	9.8
1-3 months	120	43	29.1	47	5	10.5
3-6 months	75	21	28	48	6	12.5
6-12 months	22	4	13.6*	47	3	6.3
12 months plus	8	3	37.5*	11	2	18.1*
Totals	361	132	36.5	234	24	10.2

*Included for completeness, but obviously of no significance because of the small total number involved.

TABLE IV. SEVERITY OF DIAPER RASHES BY AGE GROUPS

	POSITIVE				NEGATIVE			
AGES	M	MS	S	TOTALS	M	MS	S	TOTALS
0-1 month	9	36	16	61	21	42	12	75
1-3 months	7	31	5	43	17	49	11	77
3-6 months	8	10	3	21	21	25	8	54
6-12 months	1	2	1	4	5	10	3	18
12 months plus	–	2	1	3	3	2	–	5
Totals	25	81	26	132	67	128	34	229

M = Mild.
MS = Moderately severe.
S = Severe.

As will be noted, the percentage of recovery of Candida increases directly with the severity of the rash. The severe rashes accounted for 43.3 per cent of recoveries. Interestingly enough, infants with miscellaneous con-

yielded positive culture. From 3 to 6 months of age, recovery was made in 28 per cent of the cases. After the sixth month, there is a marked decrease in the total number of diaper rashes observed. Table IV correlates age with

the severity of the diaper rashes and again illustrates that the diaper rash problem is largely one of the younger infant.

Fig. 1 gives the seasonal occurrence of Candida. We had anticipated a higher incidence during the summer months, since the fungus thrives on moist surfaces, but this was not apparently the case during these observations.

in which the incidence of Candida is known to be high, and the multiple diagnoses group (all of which had diaper rashes), only 14 of 48 cases cultured proved positive.

Oral cultures were taken in 101 cases, and of these 51 were positive for *Candida albicans*. All 51 cases also had positive skin cultures and 36 of these infants had clinical thrush.

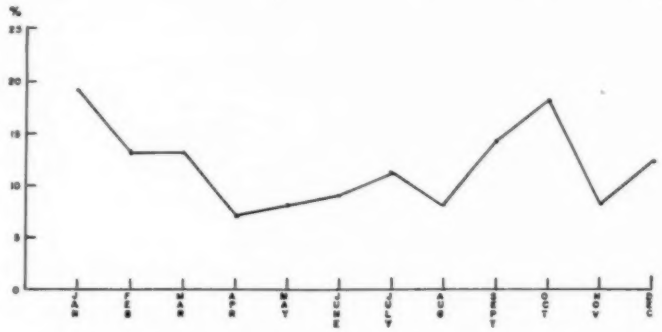

Fig. 1.—Per cent incidence of rashes positive for moniliasis by months. Total population observed 1,447 infants.

Table V, which lists the miscellaneous diagnoses observed, unless scrutinized carefully, is apt to be misleading. When one eliminates intertrigo,

TABLE V. MISCELLANEOUS DIAGNOSES

	TOTAL	N	P
Eczema	6	3	3
Contact dermatitis	2	1	1
Pustular dermatitis	3	2	1
Seborrheic dermatitis	12	9	3
Irritative dermatitis	2	–	2
Atopic dermatitis	2	2	–
Excoriated knee	1	–	1
Intertrigo	22	12	10
Miliaria	14	13	1
Omphalitis	2	1	1
Pyodermia	3	3	–
Vaginal discharge (newborn infants)	1	–	1
Multiple diagnoses*	43	18	25
Totals	113	64	49

N = Negative for Candida.
P = Positive for Candida.
* = Diaper rashes plus conditions listed above.

Diaper rashes attributable to gastroenteritis occurred in 59 instances, and in 23 cases *Candida albicans* was recovered from the rash area, an incidence of 38.9 per cent. Rashes in the diaper area, occurring concomitantly or shortly after antibiotic therapy, were encountered in 61 instances, and *Candida albicans* was recovered from the buttocks in 27 cases, an incidence of 44.4 per cent.

Cultures of the mouth, skin, and either stool or rectal swabs were taken simultaneously on a number of infants (Table VI). While these cultures were frequently repeated, we have recorded only the results when at least one positive recovery was made. The highest incidence of recovery occurred from

rectal swabs or stools, next in frequency was the skin, and last, the mouth. Sixteen of the 36 cases of clinical thrush occurred in this group.

Service of St. Vincent's Hospital before and after delivery. Serial cultures were also taken on their infants on the first, third, and sixth day after

TABLE VI. CORRELATION OF RECOVERY OF CANDIDA FROM MULTIPLE SOURCES

AGES	MOUTH		SKIN		RECTAL SWAB OR STOOLS		CLINICAL THRUSH
	N	P	N	P	N	P	
6 days plus (86 cases)*	59	27	44	42	34	52	15
1-6 days (49 newborn infants)†	43	6	39	10	39	10	1
Totals	102	33	83	52	73	62	16

*All with diaper rashes.
†No rashes.
N = Negative.
P = Positive.

TABLE VII. SERIAL CULTURES OF MOTHERS AND INFANTS

	MOTHERS		INFANTS								
			FIRST DAY			THIRD DAY			SIXTH DAY		
	PRE-P	POST-P	M	S*	R	M	S	R	M	S	R
1. L. C.									X		
2. Q. R.	X			X	X		X	X		X	X
3. H. F.										X	X
4. F. M.	X							X			
5. E. M.				#							
6. A. D.							#				
7. J. C.	X	X			X						
8. T. A.	X	X								#	X
9. D. L.	#			X							
10. V. M.								X			
11. J. P.	#			#			#	#			
12. S. E.	X			X							
13. H. A.	X	X	X	X	X	X	X	X	Signed out		
14. A. S.	X			X			X		X		X
15. H. B.	X	X		X		#	#	X	X		X
16. F. E.	#	#				#			#	#	#
17. M. G.	X					X	X		Signed out		
18. W. M.						X			X	X	
19. E. R.						#	#	#	#	#	X
20. F. T.		#									
21. J. R.	#										
22. N. F.	#	#									
23. Z. M.	X										
24. H. H.	X										
25. C. R.		#									

X = *Candida albicans.*
# = Candida species.
M = Mouth. S = Skin.
*Vernix.
Pre-P = Just prior to delivery.
Post-P = Fourth day post partum.
R = Rectal swabs.

The newborn infants who contributed one case, however, were only observed for 6 days. The older infants were observed on a day-to-day basis for at least 1 month, most frequently 3 months.

A study was made of the vaginal flora of 50 mothers at the Obstetrical

delivery. Twenty-three mothers and infants remained negative throughout the period of observation. One mother signed out the day of the delivery. In Table VII, only those cases are included that yielded at least one positive culture for Candida. Sixteen mothers yielded Candida just before

delivery, eleven of these isolates proved to be *Candida albicans*, five were Candida species. *Candida albicans* was recovered again in four of the eleven mothers on the fifth postpartum day.

30.3 per cent, and for rectal or stool cultures 36.8 per cent.

In an analysis of the results of therapy with the phenaeridane cream (0.5 per cent), only those cases who received no other ancillary therapy were utilized. Table IX correlates the degree of success with the severity of the rash in 286 cases who met the above criteria. Failures in therapy were approximately the same in all groups. Rashes that were negative for *Candida albicans* had 22.4 per cent failures, while those that were positive had 24.1 per cent failures. The data are summarized in Table X on the basis of success and failure. Attention is called to the group of severe diaper rashes where, although the series is small, it is apparent that successful therapeutic results are obtained in severe rashes significantly more frequently when

TABLE VIII. DIFFERENTIAL RESULTS ON ISOLATES

	RASHES (635)*	MOUTH (191)*	STOOL OR RECTUM (203)*	OMPHALITIS	VAGINAL DISCH.	CONTROLS (258)*	TOTALS
Candida albicans	184	58	75	1	1	18	337
Poss. *Candida albicans*	2						2
Candida species	25	2	16			2	45
Questionable or contaminated	8		1			2	11
No growth	15	2	11				28
No Candida	2		1				3
Dried cultures	1					2	3
Totals	237	62	104	1	1	24	429

*Number of cultures.
78.4 per cent of all isolates were *Candida albicans*.
10.5 per cent of all isolates were Candida species.

TABLE IX. THERAPEUTIC RESULTS OF DIAPER RASHES

	EXCELLENT		GOOD		FAIR		FAILURE		TOTALS
	N	P	N	P	N	P	N	P	
Mild	21	4	12	5	12	5	7	5	70
Moderately severe	25	17	27	23	22	14	20	15	163
Severe	3	4	4	6	9	8	12	7	53
Totals	49	25	43	34	43	27	39	27	286

N = Negative.
P = Positive.

Nine of the infants of the positive eleven mothers yielded *Candida albicans* in at least one culture from either the mouth, skin, or rectum. The organism was cultured from the mouth in four of these babies. *Candida albicans* was recovered from the mouth cultures of two babies whose mothers were negative. One of these two infants developed clinical thrush and was the only case observed in this group. No consistent pattern in the mycology was demonstrated.

Table VIII demonstrates the high incidence of recovery of *Candida albicans* (78.4 per cent) from isolates. The recovery rate for skin cultures was 27.3 per cent, for oral cultures

these rashes proved positive for *Candida albicans*. The totals, however, are not noticeably different between the negative and positive rashes, being

Table X. Summary of Therapeutic Results on the Basis of Success or Failure of Diaper Rashes

	NEGATIVE				POSITIVE			
	T	S	F	S (PER CENT)	T	S	F	S (PER CENT)
Mild	52	45	7	86	18	13	5	72
Moderately severe	94	74	20	79	69	54	15	78
Severe	28	16	12	57	25	18	7	72
Totals	174	135	39	78	112	85	27	76

78 per cent successful for the former and 76 per cent successful for the latter.

An analysis of the effect of treatment on the mycology is presented in Table XI. While the total number of

Table XI. Correlation Between Clinical Results and Effect on Mycology of Positive Diaper Rashes

	TOTALS	REVERSAL	NON-REVERSAL	PER CENT REVERSAL
Success	79	63	16	79
Failure	33	20	13	60
Totals	112	83	29	74

failure cases is small, these data would seem to indicate that success in therapy is more likely to occur when mycology is reversed.

It was virtually impossible to analyze the therapeutic results in the group of miscellaneous diagnoses (Table V), the sole exception being intertrigo. In these cases, when *Candida albicans* was recovered, there were no failures and the results were either excellent or good. There were six failures in the negative cases.

No evidences of sensitivity to the phenacridane cream were observed in the infants treated.

DISCUSSION

During the course of this study, 13 infants of the 1,447 observed fulfilled the clinical criteria of cutaneous candidiasis as described by Dobias and others.[1, 11, 12, 15, 20] Candida was recovered, however, from the skin of 205 infants and in most instances (78.4 per cent) the organism was *Candida albicans* (Table VIII). The majority of these cases were diaper rashes and, in view of the high incidence of recovery from the stools of infants, we feel that in most instances these positive cases represented stool contamination and should not be diagnosed as cutaneous candidiasis. The diagnosis of cutaneous candidiasis should be reserved for cases that present the clinical syndrome with positive cultures or who present themselves with intractable rashes and positive mycology. In the majority of cases, our positive diaper rashes were clinically indistinguishable from the negative cases; moreover, the therapeutic results were, for all practical purposes, identical in both groups of cases (Table X). The only exception to this was in the severe diaper rashes when in the presence of *positive mycology* better therapeutic results were obtained (Table X). It is quite possible that some of these severe cases represented atypical clinical pictures of cutaneous candidiasis. Conceding this point, however,

there still remains a large number of cases that produced only positive mycology to sustain the diagnosis. Oral candidiasis occurred in 36 cases and *Candida albicans* was isolated orally in 51 cases. In patients where cultures were obtained from multiple sources simultaneously, there were 86 infants who were followed for at least 1 month, in most instances 3 months, and thrush occurred fifteen times (Table VI). Included in this group are the 13 cases of cutaneous candidiasis. Our data are therefore not in agreement with those of Kozinn and associates[22] who feel that the recovery of Candida from the stools is inevitably followed by oral or cutaneous candidiasis. In fact, these findings tend to confirm the observation of Winter and Foley[8] that positive oral cultures may persist for some time without the appearance of clinical thrush. One possible explanation for our inability to correlate positive oral or cutaneous cultures with clinical thrush may be the almost universal practice in obstetrical nurseries of using some sort of prophylaxis (often gentian violet) against thrush. Presumably the majority of newborn infants admitted to the Foundling had received prophylaxis. Nevertheless, positive skin cultures, in our experience, did not invariably herald the onset of the clinical picture of cutaneous candidiasis.

The incidence of positive cultures in the 61 patients who developed diaper rashes while under short-term antibiotic therapy was 44.4 per cent, despite the fact that none of these rashes were classified as severe. This would seem to indicate that antibiotic therapy enhances the proliferation of Candida in the intestinal tract and increases the rate of recovery of the organisms.

While the number of cases in the specific groups of miscellaneous diagnoses was small, *Candida albicans* was recovered from the eczematous areas in 3 of 6 cases of eczema and in 3 of 12 cases of seborrheic dermatitis (Table V). One of the latter occurred in a 7-day-old baby with extensive desquamation over the scalp, face, and body. *Candida albicans* was recovered from all these areas. Unfortunately, the mother was not available for study; in fact, none of the mothers of the babies observed at the Foundling Hospital were available for investigation.

The phenacridane cream was, in general, equally as successful in the negative cases as in the positive. However, in the severe diaper rashes with excoriation, it showed an appreciable superiority when the rash was positive for Candida. An interesting observation was the "lag period" which occurred with this therapeutic agent. For the first 24 hours of application, very little therapeutic effect was noticeable; on the second day good results could almost be predicted, as the therapeutic benefit would be marked and obvious. We observed no irritation when the material was applied around and about the genitalia. This is in marked contrast to even half-strength Whitfield's ointment which invariably produced irritation and burning when applied to these sensitive areas. One of the disadvantages in the use of this preparation was its canary-yellow color and its staining properties. Unlike gentian violet preparations, however, it could be contained to the diaper area and did not spread. Nevertheless, because of the color and staining, the ointment should probably be used only in severely excoriated rashes.

In view of the results obtained, and the ease with which it could be removed from the affected skin, it proved popular with the nursing personnel.

SUMMARY AND CONCLUSIONS

A 2-year study involving observations of 1,447 infants was conducted to ascertain the role of *Candida albicans* in the common rashes of infancy and early childhood. There was no correlation between sex and color and the recovery of Candida from the skin. Age was an important factor in that infants under 1 month had more severe rashes and a higher incidence of rashes positive for Candida. The organism was recovered in 36.5 per cent of infants with diaper rashes and in 43.3 per cent of infants with rashes of other types. A control group of infants yielded 10.2 per cent positives. Thirteen cases presented the clinical syndrome of cutaneous candidiasis with associated positive mycology. It is unlikely that all cases of diaper rashes presenting positive mycology represent true invasion of the skin by the parasite. Thirty-six cases of thrush were observed in this series in 51 infants who showed positive oral cultures. A correlation between the vaginal cultures of mothers and the cultures of the skin, mouth, and rectum of their newborn infants could not be demonstrated in a small random series. Ten newborn infants of 49 tested showed at least one positive culture from either the skin or rectal swab; 6 of the 49 infants had at least one positive oral culture. The organism can occasionally be recovered in infants presenting themselves with diagnoses other than diaper rashes, as for example, eczema, seborrheic dermatitis, and intertrigo.

Phenacridane cream was almost equally successful in cases having either negative or positive mycology. However, it showed an appreciably superior therapeutic effect in severe diaper rashes when the mycology was positive. It was also more effective when there was evidence that the positive mycology had been reversed (Table XI). No evidences of sensitivity to the therapeutic agent were demonstrated in 361 patients who received frequent daily applications for a period of up to 10 days.

I wish to express my appreciation to the Sisters, Nurses, and house officers of the New York Foundling Hospital and St. Vincent's Hospital for their assistance and cooperation in this study.

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Some Mortality Figures 100 Years Ago—Report to the College of Physicians in Philadelphia

This early waste of life, as it applies to our own city and to other large cities in this country, will be found to depend in a great measure upon the alarming sacrifice of human life in infancy, a reprehensible immolation growing out of the distribution of evils in every community that are not only preventable, but at the same time are culpably neglected.

In this city, for the last five years, the mortality in children under five years of age will average 47 per cent. of all the deaths. In New York it is still more frightful. For fifty years the average deaths under five years have been equal to 50 per cent. of the mortality. And if for fifty years, how much more deplorable within the last few years, when in a single year, according to their own statement, "in 1853, the excess over one-half the entire number of interments of all ages in the city reached to thousands." From the City Inspectors' report for 1854, '55, and '56, it appears that 58.83 per cent. of the mortality was in infants under five years of age.

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ACUTE GASTROENTERITIS

A Review of 821 Cases Treated at the Hospital for Sick Children During the Year 1956

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ACUTE gastroenteritis as we know it today was not always so named. Forty years ago its various grades of severity and phases were regarded as entities while little attention was paid to etiology. Such diagnostic terms as "intestinal indigestion," "intestinal intoxication," "fermentative diarrhea," and "cholera infantum" were then in use. That these terms are no longer used, points to an evolution of understanding which has come about. Bacteriologic studies and the knowledge of dehydration and electrolytes have rendered them obsolete. Virology will surely help to complete our comprehension of this disorder. Of the old terms, "parenteral diarrhea" is the only one to endure, but with the increasing number of etiologic agents discovered, its use becomes ever more restricted.

This study is an attempt to appraise advances that have been made and to gauge the relative importance of various etiologic agents in gastroenteritis.

Wolfish[1] made a similar study of gastroenteritis at this hospital during 1951 and 1952. Comparisons with that series, wherever profitable, are made in this paper.

From the Department of Paediatrics, University of Toronto, and the Hospital for Sick Children, Toronto, Canada.

MATERIAL STUDIED

The present series consists of the 821 children of all ages who, during the 12 months from January through December, 1956, either were admitted with gastroenteritis or developed it during their stay in hospital.

Reference to our 1956 inpatient statistics (all services), under the international classification, reveals the data shown in Table I. Only patients under the age of 2 years—641, or 78 per cent of 821—were studied in detail, since it had been shown by Wolfish[1] that most fatalities and difficulties with diagnosis and treatment occur within this younger age group. The records of these 641 patients were studied and reclassified on the basis of stool culture results and the presence or absence of disease other than gastroenteritis.

THE INFLUENCE OF SEASON AND AGE OF PATIENTS

The month-by-month incidence of gastroenteritis among the 641 patients under the age of 2 years is depicted graphically with a broken line in Fig. 1.

Also shown in Fig. 1 are the monthly incidence patterns of the component classification Groups I and II (thick and thin lines respectively), especially created in this study.

Table II indicates the derivation of Groups I and II. The rationale for this classification is an attempt to study separately those patients who might be suffering from viral as opposed to bacterial or parenteral gastroenteritis. Group I (Table II), therefore, includes only those infants in whom no cause could be found for gastroenteritis either from stool bacterial culture or from infection elsewhere in the body. Even patients from whom bacteria of doubtful pathogenicity were cultured from the stool were excluded from Group I.

Surprisingly, Fig. 1 shows that gastroenteritis of all types was most prevalent during the winter months. The month of September, the traditionally "dangerous mouth" for gastroenteritis

TABLE I

DIAGNOSIS	PRINCIPAL	SECONDARY
Typhoid	0	2
Dysentery, bacillary	12	7
Gastroenteritis and colitis, except ulcerative:		
Gastroenteritis due to diet*	6	1
Gastroenteritis due to infection	236	109
Gastroenteritis due to unknown cause	404	31
Colitis, acute*	18	13
Enteritis, acute	13	10
Enterocolitis, acute	5	3
Parenteral diarrhea	0	10
Grand Total	880	
Patients' records studied	842	
†Patients included in series	821	

*These patients were not considered apt to the problem and were therefore excluded from this series.

†A further 21 of the remaining 842 patients were discarded after study of their charts had revealed that they did not suffer from diarrhea at any time.

TABLE II

GROUP	CHARACTERISTICS	NUMBER OF PATIENTS	PERCENTAGE
I	"Usual flora" reported from stool culture and no clinical or bacteriologic evidence of disease other than gastroenteritis detected	293	46
IIA	"Usual flora" reported from stool culture but also suffered from some clinically or bacteriologically demonstrated pyogenic infection outside the gastrointestinal tract (i.e., otitis media, tonsillitis, meningitis, pneumonia, etc.). This group can be termed "parenteral gastroenteritis"	104	15.9
IIB	No stool culture obtained Mostly "parenteral gastroenteritis" secondary to clinical upper respiratory tract infection	27	4.2
IIC	Accepted pathogenic bacterin cultured from the stool: i.e., Salmonella, Shigella, and pathogenic *E. coli* groups	51	7.9
IID	Organisms of debatable pathogenicity isolated from stool cultures: i.e., Proteus, Pseudomonas, Paracolobactrum, Streptococci, *Bacillus anitratum* and Providence group	100	15.7
IIE	Pyogenic staphylococci isolated by stool culture	66	10.3
	Totals	641	100

in infancy, appeared to be relatively trouble free when compared with December, January, and February. Having discussed this seemingly unusual finding with pediatricians on the staff of the hospital, the author found it to be their impression that the very young infants accounted for most of the gastroenteritis cases during September and that, although many infants were affected, few required hospital admission. A series of graphs was therefore constructed to show the month-by-month incidence of gastroenteritis in progressively younger age groups (Fig. 2). When only those infants below the age of 1 year (Fig. 2, top left) were studied, the number of Group I cases, possibly of viral etiology, was less than those in Group II, but the September peak was more marked than it had been in Fig. 1. With p r o g r e s s i v e l y younger age groups, down to those under the age of 3 months (Fig. 2, bottom right), the Group I gastroenteritis patients finally dominated the scene with a peak incidence in September which, for the first time, was higher than Group II gastroenteritis at any time of year.

A very definite difference has thus been demonstrated between Groups I and II gastroenteritis both as to the times of year at which they are most prevalent and as to the age groups most involved. This lends support to the impression that the etiology of Group I gastroenteritis differs from those groups where bacteria play a part. By definition, Group I patients were free of bacterial infection not only in the intestines, but also elsewhere in the body. It would appear, therefore, highly likely that viral infections were involved in the epidemic of diarrhea during the months of September and October, and that it attacks particularly infants under the

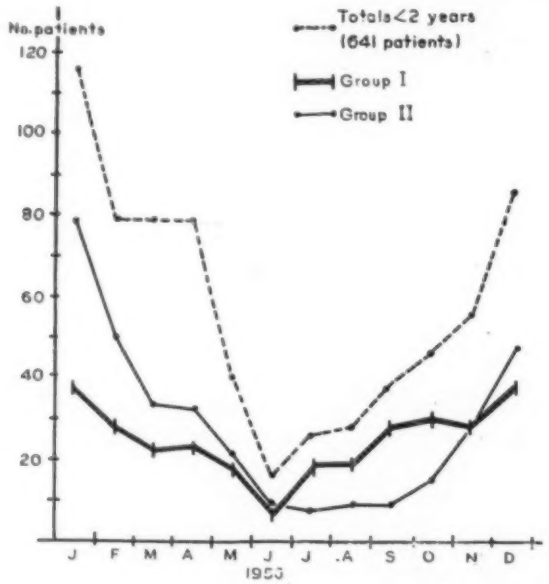

Fig. 1.—Monthly incidence of gastroenteritis in those under the age of 2 years.

age of 3 months. Diarrhea at other times of year and in infants older than 3 months was more often due to bacterial infection, enteral or parenteral. Infants under the age of 3 months did not appear to have been very susceptible to gastroenteritis from bacterial infection, nor so prone to bacterial infections during the winter months. In spite of the very young age group predominantly involved, mortality was 19.9 per cent of the admissions (Groups IIA and IIB in Table II).

THE BACTERIOLOGY OF THE STOOLS

Table III gives a breakdown of the major categories of stool reports of the patients under the age of 2 years. Only 4.2 per cent of this group escaped having stool cultures, a considerable improvement on the figure in previous years. The pyogenic staph-

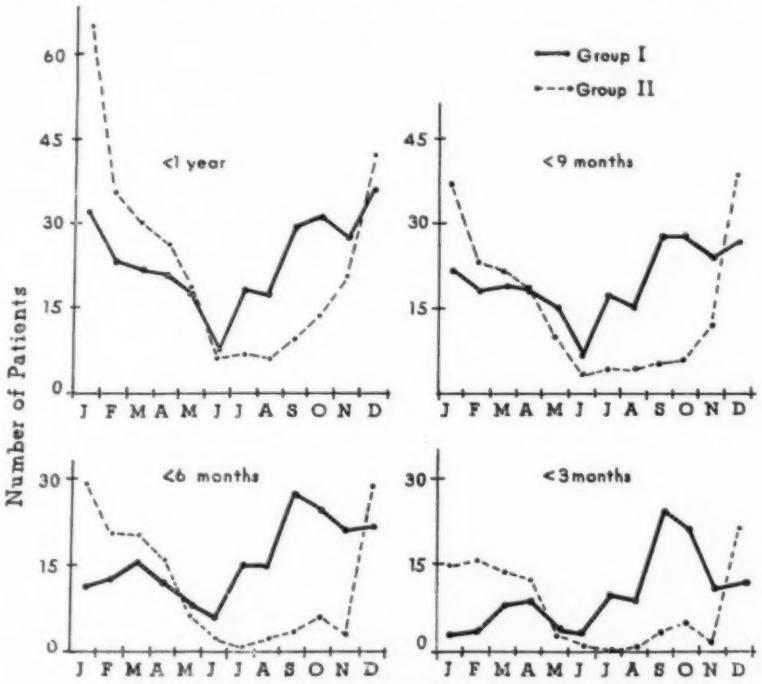

Fig. 2.—Monthly incidence of gastroenteritis, 1956, at different ages.

not associated in this series with the Group I, presumably viral, gastroenteritis, but rather with the bacterial enteritis group.

"Parenteral gastroenteritis," a diagnosis of exclusion as far as stool culture was concerned, but one definitely associated with infection outside the gastrointestinal tract, occurred in

ylococci are classified separately from the organisms of doubtful pathogenicity and the accepted pathogens, because, as will be seen later, they accounted for a large share of the mortality while not generally being regarded as classically "pathogenic" in respect of gastroenteritis.

Table IV shows a more detailed analysis of bacteria reported in the

stool cultures of the 217 patients under the age of 2 years whose stool cultures grew organisms mentioned in addition to the "usual flora."

rhea would have one believe that the fall epidemic is largely due to the greater ease with which bacterial pathogens multiply during warm weather.

TABLE III

	NUMBER	PER CENT
Patients under the age of 2 years	641	
No stool culture taken in the above group	27	4.2
"Usual flora" reported on the stool culture	397	61.9
Some organism(s) (pathogens and doubtful pathogens) reported in the stool culture	217	33.9
		100

Table IV also indicates the month-by-month incidence for all organisms and again underlines the fact that January and February are the months when infants are most frequently attacked by bacterial gastroenteritis. Traditional concepts of infantile diar-

This factor certainly did not operate in the year 1956 among patients admitted to this hospital. The coldest months of the year were those in which bacterial infection accounted for the majority of gastroenteritis cases.

Fig. 3 is a graphic representation of

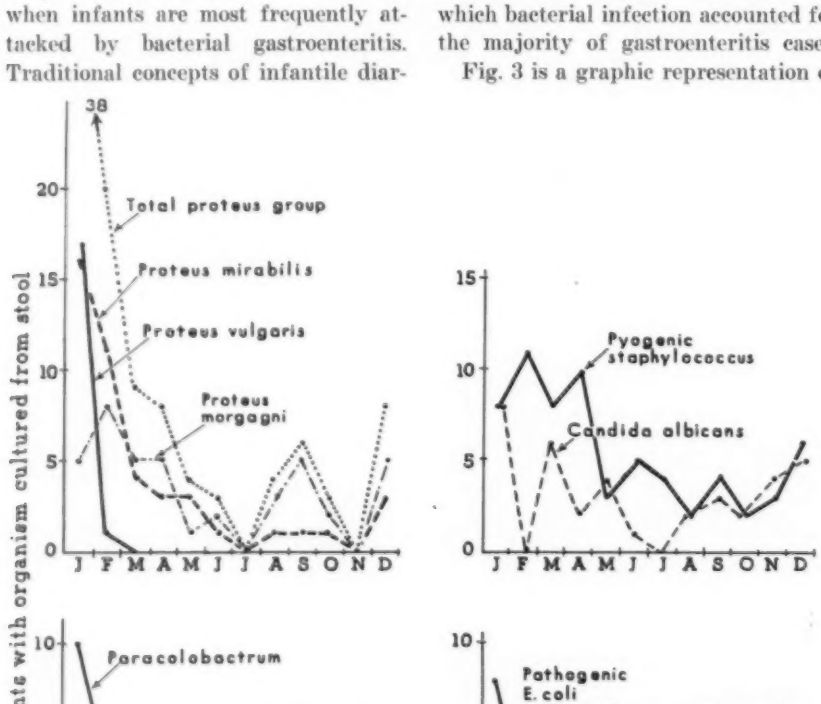

Fig. 3.—Micro-organisms, 1956.

TABLE IV. MONTH BY MONTH INCIDENCE OF VARIOUS ORGANISM GROUPS IN STOOL CULTURES

MICROORGANISM	TOTALS	MONTHS OF THE YEAR, 1956											
		JAN.	FEB.	MARCH	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
Proved pathogens													
Salmonella group	28	8	1	2	2	0	1	2	2	4	1	3	2
Shigella group	4								1			2	1
E. coli serotypes	16	4	1	1	1	1		1	2	3	2		
Totals	48	12	2	3	3	1	1	3	5	7	3	5	3
Pyogenic staphylococcus:	66	8	11	8	10	3	5	4	2	4	2	3	6
Suspected pathogens:													
Proteus group	103	38	20	9	8	4	3		4	6	3		8
Pseudomonas group	25		6	2	1			1	3	3	3	3	3
Paracolobactrum group	42	10	4	6	2	2	2	1	5	4	1	1	4
Candida group	37	8		6	2	4	1		2	3	2	4	5
Streptococci	6	1	1		1					1		1	1
Bacterium anitratum, etc.	6	1			2		1	2					
Providence group	1								1				
Totals	220	58	31	23	16	10	7	4	15	17	9	9	21

The numbers total more than the 217 patients from the stools of whom these organisms were cultured because several bacteria were mentioned together in many single reports.

the month-by-month incidence of various bacteria in those under the age of 2 years in this series.

It is interesting to note the inverse incidence of the pyogenic staphylococcus and *Candida albicans* (Fig. 3) which existed from February through August and their parallel incidence for the remainder of the year. Whether or not the figures upon which this graph has been constructed are statistically significant to an extent allowing conclusions to be drawn is debatable. It is known that both organisms flourish in the intestines where the normal flora has been modified and reduced by antibiotic therapy. It might appear from Fig. 3 that when the pyogenic staphylococcus flourishes, conditions for the growth of *Candida albicans* are less favorable, and vice versa, but only during the months before September. Thereafter, conditions which favor or inhibit both in the same direction would appear to have existed. As shown earlier, the prevalent type of gastroenteritis from September onwards was of a different nature and not dependent upon bacterial infection. It is interesting to speculate that this other type of infection, possibly viral, created conditions equally favorable or unfavorable to both organisms.

The lower right hand graph in Fig. 3 demonstrates the incidence through the year of the undisputedly pathogenic bacteria. The highest incidence was in January, but there was a lesser rise of longer duration during the fall. Organisms of debatable pathogenicity are similarly plotted in the graphs on the left of Fig. 3. Again, much the same sort of pattern is followed, although, in the Proteus family of organisms, the January and February incidence is much higher than in any other group of organisms. *Proteus vulgaris* appeared only in the months January and February and at no other time of the year. This dramatic and short-lived appearance of *Proteus vulgaris* occurred in 18 per cent of all the stool cultures of those patients suffering from Group II gastroenteritis (defined earlier in this paper). If the Proteus organisms were accepted gastroenteritis-producing pathogens, one would say that they largely accounted for the very high peak in incidence of gastroenteritis during the months of January and February. However, it can be argued that there were more cases of gastroenteritis during those months and, therefore, more stools from which Proteus organisms could be cultured. Nevertheless, *Proteus vulgaris* was found only during January and February, coinciding with an explosive increase in the number of gastroenteritis cases. In January it was present in 17 of the 28 Group II patients in excess of the February Group II patients. At other times of the year, when the incidence of Group II gastroenteritis remained at a consistently lower level, *Proteus vulgaris*, unlike other members of the Proteus group, disappeared entirely from the stools. The data presented might suggest that *Proteus vulgaris* is a pathogenic organism causing gastroenteritis, but of course, it cannot be taken as conclusive evidence that this is so. Local epidemics of gastroenteritis due to a certain organism have been known to occur in a community from time to time but have not necessarily always recurred when that organism has reappeared. Also, it is known that the normal intestinal flora in a community

varies from season to season and year to year without necessarily disturbing health.

The pathogenic *E. coli* serotypes were cultured from the stools of 16 patients under the age of 2 years. There were 21 patients of all ages of childhood whose stools grew this organism during the year (Table V).

TABLE V. NUMBER OF PATIENTS TREATED FOR PATHOGENIC *E. coli* INFECTIONS DURING THE YEARS 1954, 1955, AND 1956*

E. coli SEROTYPE	1954	1955	1956
0111 B4	96	14	3
055 B5	11	6	1
026 B6		7	6
0125 B15		1	6
0126 B16		3	5
Totals	107	31	21

*Patients readmitted with same infection are counted only once.

It is interesting to compare the incidence in 1956 of pathogenic *E. coli* infections with that in previous years and to note the steady and most marked decrease, which has been greater than that in the Salmonella and Shigella infections (Table VI). This decrease has occurred in spite of the fact that further members of this group have been recognized each year, and that it depends almost entirely upon the reduction of hospital cross-infection, the means by which this organism formerly spread among the younger infants in open wards.

DEATHS

The 1956 gastroenteritis mortality of 0.97 per cent (0.94 per cent for those under the age of 2 years) is a considerable reduction on that of former years. Table VII indicates how these figures were derived.

TABLE VII

RELATIONSHIP OF GASTROENTERITIS TO DEATH	ALL AGES		UNDER 2 YEARS	
	NO.	%	NO.	%
1. Primary cause	3	0.36	3	0.47
2. Possible accessory cause	5	0.61	3	0.47
3. Unrelated to cause	6	0.73	6	0.94
Totals	14	1.70	12	1.88
Mortality discarding Group 3	8	0.97	6	0.94

Gastroenteritis admissions (patients of all ages) 821.

Deaths in the above group 14 (1.70 per cent).

Gastroenteritis admissions (patients under age of 2 years) 641.

Deaths in the above group 12 (1.88 per cent).

Staphylococcus pyogenes had been cultivated from the stool or the blood in 4 of the 6 patients under the age of 2 years where gastroenteritis was either a primary or a secondary cause.

TABLE VI

	AGE	NUMBER OF PATIENTS 1954	NUMBER OF PATIENTS 1955	NUMBER OF PATIENTS 1956
E. coli	Under 1 year	89	23	13
	1-2 years	17	3	3
	Over 2 years	1	5	5
	Total	107	31	21
Shigella	Under 1 year	16	11	3
	Over 1 year	48	28	12
	Total	64	39	15
Salmonella	Under 1 year	12	20	20
	Over 1 year	14	20	10
	Total	26	40	30

Antibiotics had been given for several days prior to the onset of violent diarrhea in 3 patients and it is assumed that this treatment had so modified and depleted normal intestinal flora as to encourage growth of antibiotic-resistant staphylococci.

teritis was treated with a retention enema of fresh, normal feces suspended in protein milk. This coincided with the appearance of a more normal intestinal flora and recovery from the enteritis. The value of this procedure could, with profit, be assessed in a ser-

TABLE VIII. ANALYSIS OF DEATHS IN THOSE UNDER 2 YEARS OF AGE

AGE	STOOL CULTURE	OTHER FACTORS
	Deaths Primarily Due to Gastroenteritis	
2 months	*Staph. pyogenes* had replaced the normal gut flora	Dystrophic on admission; mongol; milk allergy. Had been treated with neomycin for 8 days for gastroenteritis before onset of explosive diarrhea
4 months	*Shigella flexneri* (and blood culture)	Patient admitted moribund. Had arrived 1 day previously from Italy where 4 siblings had died in infancy from gastroenteritis. Organism was sensitive only to Polymyxin B
11 months	*Paracolobactrum coliforme*	Cerebral agenesis. Had vomited since birth
	Deaths Where Gastroenteritis Was Possibly an Accessory Factor	
1 month	*Staph. pyogenes*	Staphylococcus pneumonia and enteritis appeared after 11 days in hospital with neomycin treatment for gastroenteritis with *Proteus morgagni* cultured from stools
1½ months	*Staph. pyogenes*	Patient had undergone bilateral mastoidectomy 6 days previously and subsequently developed meningitis and had been treated for 10 days with penicillin and streptomycin before gut flora became replaced by *Staph. pyogenes*
13 months	*Staph. pyogenes*	The patient had been treated for 6 days for tonsillitis with penicillin and streptomycin when staphylococcus pneumonia and enteritis developed. The diarrhea did not respond to Chloromycetin and neomycin

Two deaths occurred in patients from whom *Staphylococcus pyogenes* was not cultured from the stool and the circumstances are readily understandable on inspection of Table VIII.

Mortality in this series would appear to be at an almost irreducible minimum with present methods of diagnosis and treatment. These deaths were really more related to the problem of the antibiotic-resistant staphylococcus than to gastroenteritis per se. Further progress in this field awaits new antistaphylococcal remedies and methods for preventing the growth of this organism. Recently, one patient in this hospital with severe antibiotic-resistant staphylococcal enies of cases. Patients developing resistant staphylococcal infections were transferred to the isolation unit and this undoubtedly has reduced cross infection within the hospital.

During 1953, and presumably earlier when these organisms were unrecognized, there was considerable morbidity and mortality from pathogenic *E. coli* gastroenteritis. Most cases had resulted from cross infection among infants in open wards. This serious situation, unabated by all therapeutic measures, continued until later in the year when, for the first time in this hospital, a new general ruling regarding isolation of all cases of gastroenteritis was made This ruling applied

without exception to all cases of gastroenteritis on admission and also to all those developing in hospital. The reduction in incidence of *E. coli* morbidity (Table V) is largely attributable to this measure, which has also prevented cross infection with all other easily transmissible organisms.

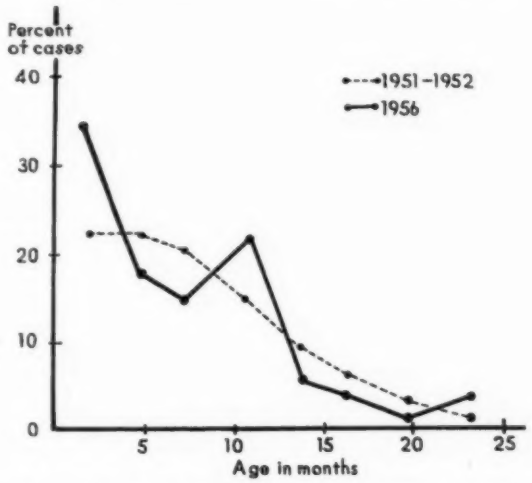

Fig. 4.—Comparison of incidence of gastroenteritis at different ages in the 1956 and the 1951-1952 series.

It will be shown later that there has been a large increase in the number of patients investigated by stool culture. Undoubtedly, this has allowed more efficient detection of infections with pathogenic bacteria and has played an important part in the reduction of mortality.

Permanent morbidity in the form of mental deficiency, resulting from convulsions during treatment of gastroenteritis, is probably becoming a more serious problem numerically than mortality from gastroenteritis. Convulsions occurred while the body fluid and electrolyte pattern were disturbed and during treatment of this disturbance. This problem forms the substance of a paper shortly to be produced by the author.

COMPARISON WITH AN EARLIER STUDY

Wolfish[1] reviewed the 518 inpatients treated for gastroenteritis in this hospital during the 18-month period from July, 1951, through December, 1952. Unfortunately, his series contained admissions during only one winter and two falls, thus making comparison with the present series difficult. Further, his series included bacteriological studies on patients of all ages, whereas the present series, in this respect, only includes those under the age of 2 years.

Earlier investigators[2, 3] have found a seasonal variation in incidence, most of them in late summer and early fall. In Toronto, September was formerly the month of highest mortality and morbidity from gastroenteritis but, in Wolfish's series, the cases in summer only slightly exceeded those during the winter months. The situation at this

hospital has now been completely reversed, and, as has been shown in the present series, the winter months of January and February are those of highest incidence. The September peak of incidence has disappeared in all age groups other than that of infants under the age of 3 months and in whom the type of infection would appear different to that mostly responsible in winter.

Gastroenteritis would still appear to be a disease of infancy, with the greatest incidence in those under the age of 1 year. The age incidences are compared in the 1951, 1952, and 1956 series (Fig. 4). Study of Fig. 4 reveals a second smaller rise in incidence in the 9- to 12-month age group in the 1956 series which was not apparent in the 1951 and 1952 series. This might be accounted for by the fact that the 1951 and 1952 series included only one January-February period as against two falls. It will be recalled that in the present series the worst outbreak of gastroenteritis occurred among the older infants during January and February, and its importance in 1951 would have been relatively halved when compared with the total incidence among the younger infants in the two falls. This gives an erroneous impression of age incidences and artificially smoothes the age-incidence curve in the earlier series.

Regarding etiology, Fig. 5 illustrates the greater percentage of patients from whom stool cultures were taken in the recent as compared with the earlier series. In both series, roughly the same order of number of cultures were reported to contain some bacteria other than the "usual flora." In contrast, cultures growing only "usual flora" were four times more frequent in the present study. Had more patients been investigated by culture in the earlier series, a greater percentage might have been reported to grow only

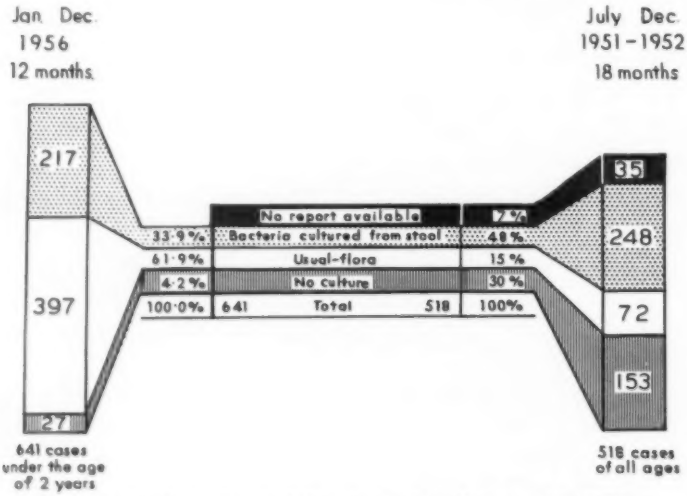

Fig. 5.—Comparison of two studies in the Hospital for Sick Children.

"usual flora." The criteria by which certain patients were selected for stool culture in the earlier series are not known, but presumably those cases of gastroenteritis not obviously "parenteral" and of a more serious nature would have been more likely to have had cultural investigation. In this way, the larger percentage of stools which yielded accepted or debatable pathogens rather than "usual flora," can be explained.

wider range of antibiotics would also reduce the number contracting this complaint.

Fig. 6 illustrates the marked similarity in the two series between the frequency of occurrence of various organisms in the stool cultures. In both series (Fig. 6), the percentages total to more than 100 because more than one organism was frequently reported in a single stool. The only outstanding difference between the series in

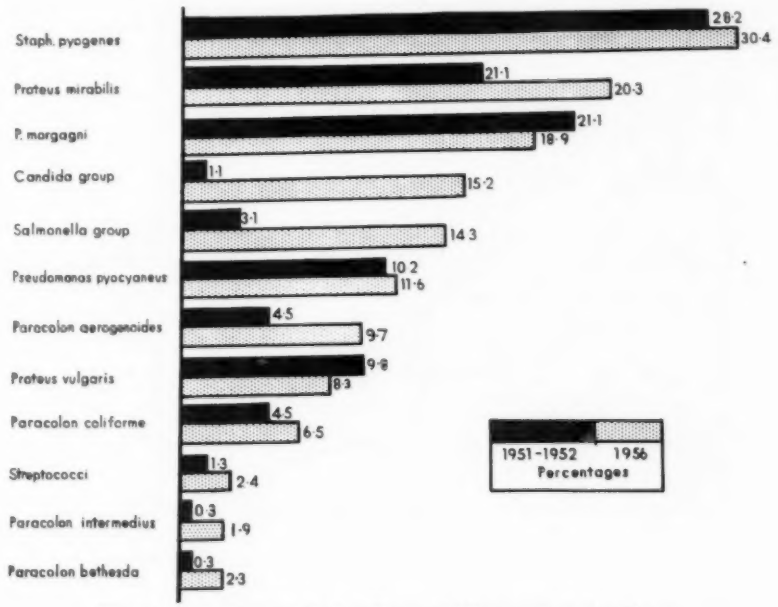

Fig. 6.—Percentage of stool cultures yielding various organisms.

Parenteral gastroenteritis occurred in only 20.1 per cent of cases in the present series as compared with 40 per cent in the earlier series. This reduction could be attributed in part to the greater percentage of patients investigated by stool culture, thereby revealing that more of them were due to intestinal infection. More rapid cure of upper respiratory infections with a

this respect was in the case of the Salmonella and Candida groups. Annual variations with Salmonella infections are to be expected in such a community as Toronto, where immigration from Southern Europe accounts for a large part of the growing population. Broad-spectrum antibiotics were much more extensively used in the 1956 than in the 1951, 1952

series, and this may well be related to the increase from 1.1 per cent to 15.2 per cent of stool cultures reported to grow *Candida albicans.*

Mortality in this hospital from gastroenteritis fell from 3.3 per cent in the 1951 and 1952 series to 0.97 per cent in 1956. More than one third of the 1951 and 1952 deaths occurred within 1 hour of the infants' admission and before treatment was given. Those infants were found to be suffering from profound shock and dehydration. No bacteriological study was made of the fatal cases in the 1952 series, but it seems probable, in retrospect, that much of the mortality was due to epidemic and hospital cross-infection with pathogenic *E. coli* serotypes, which were not studied in those days.

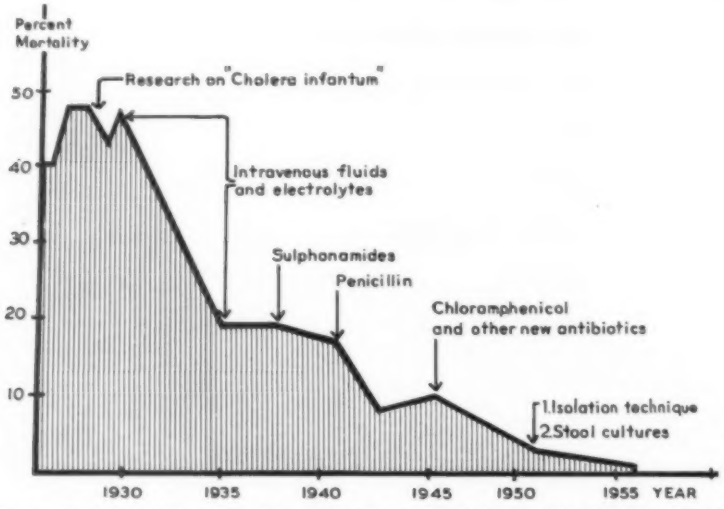

Fig. 7.—Gastroenteritis. Mortality rates at the Hospital for Sick Children, 1926-1956.

MORTALITY DURING THE PAST 30 YEARS

Great progress has been made in this hospital during the last 30 years in the treatment of gastroenteritis (Fig. 7). Before 1930, between 40 and 50 per cent of gastroenteritis patients died. This mortality was more than halved during the next 5 years by the use of intravenous fluids and electrolytes in the correction of dehydration. Thereafter, no further advance was made until the Sulfonamides were used in the latter 'thirties. Their favorable effect was not so marked as that of penicillin which became available during the early 'forties, bringing the mortality rate down to 10 per cent in 1943. With the development of penicillin-resistant organisms, presumably, there was a slight rise in the mortality rate until 1945. Part of the improvement since 1949 must certainly be ascribed to the introduction of chloramphenicol and other broad-spectrum antibiotics.

Although the greater than 300 per cent fall in mortality from the 3.3 per cent in the 1951 and 1952 series to less

than 1 per cent in the 1956 series does not appear so dramatic in Fig. 7 as that which occurred between 1930 and 1935, it does in fact represent a further great improvement. This advance can be largely attributed to immediate isolation of all gastroenteritis cases whether admitted to hospital as such or developing by cross-infection after admission. The pathogenic *E. coli* organisms were undoubtedly responsible for a hard core of infections among the smaller infants prior to the institution of the isolation technique. Coincident with this improvement, a much larger proportion of patients have been investigated by stool culture, and undoubtedly this has helped in the detection of those cases due to undisputedly pathogenic organisms which require specific antibiotic treatment. Maintenance of the present low mortality figure depends upon such painstaking methods.

We are left with a hard core of deaths in which gastroenteritis per se is not the primary feature. Most of the deaths in the 1956 series were due to staphylococcal enteritis superimposed upon some other serious condition which might well have caused death on its own account. Further advance in mortality reduction would appear to depend upon antistaphylococcal remedies while maintaining our present attitudes toward isolation and stool culture in all cases.

SUMMARY AND CONCLUSIONS

1. Eight hundred and twenty-one cases of acute gastroenteritis were treated in the Hospital for Sick Children, Toronto, during the year 1956. The increase in number over that in previous years could be attributed to the growth in population of this city.

2. The seasonal incidence, once greatest during the fall, is now greatest during the months of January and February.

3. Only in infants below the age of 3 months was there a maximum incidence during the fall. This peak in incidence differed from that occurring in other age groups and at other times of the year in being associated neither with gut infection with unusual bacterial flora nor with parenteral infection. Possibly, this outbreak of gastroenteritis during the fall might have been due to a virus infection. It is suggested, therefore, that the search for viral agents causing gastroenteritis might, with economy, be restricted to infants under the age of 3 months and during the months of the fall.

4. Only 7.9 per cent of the cases in this series were associated with an accepted bacterial intestinal pathogen. Many more were associated with organisms of debatable pathogenicity. Evidence produced raised the possibility that *Proteus vulgaris* might be a pathogenic organism, and might have largely accounted for the increase in number of gastroenteritis admissions to this hospital during the months of January and February in 1956.

5. Analysis of the mortality figures revealed that gastroenteritis per se was no longer so important a factor as antibiotic-resistant staphylococcal infection.

6. Reduction in mortality since the 1951 and 1952 series was largely achieved as the result of isolation of all patients and the investigation of more patients by stool culture. These measures have virtually eliminated

hospital cross-infection with pathogenic *E. coli* organisms which previously accounted for a large share of both morbidity and mortality.

7. Mortality from gastroenteritis will probably become a lesser problem than permanent cerebral damage resulting from convulsions during a state of dehydration.

8. It is realized that all findings reported in this paper apply to this locality during the year 1956 and will not necessarily apply to other localities or in other years.

I wish to express my appreciation to Professor A. L. Chute, Dr. T. E. Roy, the Staff of the Department of Visual Education, and Miss Laura Scott of the Hospital for Sick Children for their advice and assistance in the preparation of this paper.

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Blood-Letting

Dr. Sangrado has migrated from Spain to Naples, and flourishes there in a manner which must convince Dr. Markham that the Blood-letting Controversy has not even reached the ears of that charming capital. The correspondent of the *Times* informs us that no fewer than 30,000 Neapolitans have been lately bled. For what? asks the astonished reader. Is there an epidemic of pneumonia? Are all the people grown apoplectic? Has political excitement driven the blood to the Neapolitan head? Nothing of the kind; the Neapolitan subjects of King Bomba have been bled for—the earthquake! Blood-letting, it appears, is the invariable specific there for any kind of fright; and the rocking of walls in this Southern Paradise was immediately followed by the extraction, from gentle and simple, of 30,000 pints of blood! . . . Without doubt, the intelligent physicians of that favourite capital, the resort of invalids from all parts of Europe, know as well as Dr. Watson does how absurd such a fashion is; but it must be remembered, that it is only the few who rise superior to the prejudices of the age.

From an EDITORIAL IN THE BRITISH MEDICAL JOURNAL
JANUARY 9, 1858

EMPYEMA IN CHILDREN

A Twenty-five-Year Study

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Atlanta, Ga.

FROM the time of Hippocrates, who first treated empyema surgically, to modern times, a voluminous literature has appeared. The medical profession has made a continuous effort to understand and to manage this clinical entity. The present paper reviews 133 cases of acute, nontuberculous empyema in children, occurring in the Henrietta Egleston Hospital for Children for the twenty-five years, 1932 through 1956. It seems probable that this study covers the period of the practical extinction of empyema as an important thoracic disease. While the antibiotics are not effective in combating the condition itself, they have been strikingly effective in preventing its occurrence. Unless new, resistant bacterial strains develop faster than do the new antibiotics, 1947 should mark the essential closing of this chapter of the history of thoracic surgery. Only four cases have occurred in the Egleston Hospital since that date and none has proved fatal.

A total of 26,651 children under the age of 14 years entered the Egleston Hospital in the twenty-five years studied. During this period, admissions were relatively constant, averaging 1,066 per year. Neither staff nor policy shifted drastically during this period.

One hundred and thirty-three proved cases of acute empyema were seen in the Hospital. The admissions by years (Fig. 1) show that the incidence is not constant. The fluctuations reported by Heuer[1] and Clagett and Shepard,[2] together with our cases, suggest that there is a cyclic variation which reached a peak in 1925-1927 and again in 1937-1939. Heuer suggests that the cycle parallels that of the virulence of pneumonia.

The high incidence in 1944 during an expected decline is due to five cases of staphylococcus infection, the greatest number in any one year. Staphylococcus and pneumococcus virulence probably vary independently, greatest severity resulting when both show high virulence at the same time. Improved prophylaxis and therapy have obliterated all traces of cycles in recent years, although there is some evidence that we may expect a new rise in staphylococcus virulence.

As would be expected, there is a seasonal change in incidence as well. Nearly three-fourths (72.2 per cent) of the cases occurred from December to May. More surprising was the finding that the mortality rate was lower when incidence was the greatest. The

From Henrietta Egleston Children's Hospital, St. Joseph's Infirmary, Atlanta, Ga., Department of Anatomy, Emory University, Ga., and The Piedmont Hospital, Atlanta, Ga.

winter and spring cases had a mortality of 12.5 per cent while the June to November cases, though fewer, had a mortality of 27.7 per cent.

TABLE I. DISTRIBUTION OF INCIDENCE AND MORTALITY BY AGES AND SEX

AGE (YEARS)	MALE		FEMALE	
	INCIDENCE	MORTALITY	INCIDENCE	MORTALITY
13	–		1	
12	–		–	
11	2		2	
10	–		–	
9	4		3	
8	1		5	
7	7	1	2	
6	7	–	4	
5	3	–	4	–
4	11	–	6	2
3	15	1	2	–
2	12	–	11	3
1	12	5	5	3
0	10	4	4	3
Totals	84	11	49	11

Distribution by age and sex is shown in Table I. The youngest child was 5 days old and the oldest 13 years (the upper age limit for admission to the hospital). Slightly more than half (53 per cent) were under 4 years of age.

The sex distribution in empyema is unequal but remarkably constant for a number of series from the literature. It is characteristic of the disease (Table II).

TABLE II

	CASES	% MALES
Our series (Atlanta, 1932-1956)	133	63.1
Hertzler, Miller, and Tuttle[3] (Detroit, 1949-1953)	41	58.6
Spence[4] (New York, 1920)	204	60.8
McNeil et al.[5] (Edinburgh, 1928)	89	59.5
Steinker[6] (Akron, 1920-1932)	310	60.0
	777	60.6

In our series, the difference in incidence is statistically significant ($p < 0.005$). The mortality does not reflect this difference in incidence. Eleven children of each sex died. The cases are too few for statistical confirmation

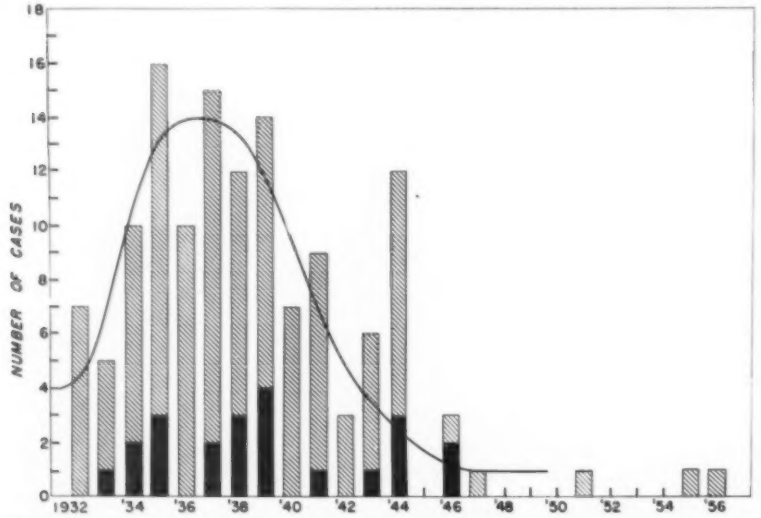

Fig. 1.—Incidence and mortality of empyema, 1932-1956. The bars represent number of cases; the solid portions represent the number of deaths. The line indicates the probable trend of the incidence.

($p < 0.2$), but it has been reported by Rienhoff and Davison[7] in their series as well.

While the incidence and mortality decrease rapidly with age in our series, it must be remembered that they rise again in the 41-50-year age group[1] and decline again in still older patients. It is thus a disease of both infancy and middle life, with a lowered incidence after 10 years and before 40 years.

Because of this pattern, we have divided our cases into those under 2 years of age, where the mortality is the greatest, and those 2 years or over. There were 31 cases under 2 with a mortality of 48.4 per cent, and 102 cases of older children with a mortality of 6.9 per cent. The over-all mortality of the series was 16.5 per cent. Because of this great decrease in mortality with age, it is not possible to compare our mortality figures with those from other series without the tedious method of reducing each series to some standard age composition. It may only be said that our percentage of fatal cases does not seem to be out of line with figures reported elsewhere for the prechemotherapy period. Hudson[8] gives a survey of the mortality in a number of series up to 1930.

No significant difference in either incidence or mortality is associated with the side on which the empyema occurs. In 10 of our cases, both sides were involved. Although Graham, Singer, and Ballon,[9] p. 134, state: "When therefore, a bilateral empyema is present, the presumption is strong that the . . . organism is a hemolytic streptococcus," in only one of our cases was this so. Five were pneumococcus, one staphylococcus, and one *Esch. coli;* two were mixed and one sterile. Of the ten, seven died. In infants under 2 years, bilateral empyema was invariably fatal. The condition was present in two of our youngest patients, one 5 and one 12 days old. Our incidence (7.5 per cent) of bilateral involvement is greater than that usually reported. See Keyes[10] for incidence in other series.

In 112 cases where white blood cell count at time of admission was reported, all whose counts were under 8,000 died. The mortality decreased with increasing height of the count, prognosis being most favorable for those with a white count in the 12,000-20,000 range. Higher counts were less favorable. Rienhoff and Davison[7] found similar results, although their lowest mortality rate occurred in the 20,000-30,000 bracket. Failure of the white cell count to rise is a very poor prognostic sign in empyema as in other infections.

The time elapsing between onset and admission to the hospital might be expected to influence the mortality from the disease. It does so in an unexpected manner (Table III). Early diagnosis does not reduce mortality. Half of the deaths in our series occurred within one week of onset, but

TABLE III. DURATION OF DISEASE PRIOR TO ADMISSION: INCIDENCE AND MORTALITY

WEEKS PRIOR TO ADMISSION	NUMBER OF CASES	NUMBER DIED
Unknown	9	0
12	1	0
9	1	0
8	5	0
7	0	0
6	4	1
5	5	0
4	12	3
3	19	3
2	28	4
1	47	11
	131	22

only slightly over one-third (35.6 per cent) of the patients were admitted that soon. One of our cases ran for six months before hospitalization. There is little doubt that virulence of the infection varies, and that the mortality rate is higher in those patients in whom the disease progresses most rapidly. These findings must not be taken to condone delay in admission or operation.

In only 5 cases was there absence of fever and in only one was there no cough. Fifteen had no concomitant upper respiratory infection. While pain was reported from more patients who recovered than who died, the age of many of them precludes the imputation of much significance to this sign.

Table IV indicates the distribution of antecedent infections. Pneumonia

TABLE IV. INFECTIONS PRECEDING THE ONSET OF EMPYEMA

INFECTION	NUMBER OF CASES
Pneumonia	65
Upper respiratory infection only	36
Measles	7
Whooping cough	3
Tonsillitis and mastoid	1
Abscesses elsewhere	3
No prior infection	19

leads the list, as might be expected, with an incidence of 48.9 per cent. More surprising are the 19 cases (14.3 per cent) reported as having no prior infection. Absence of known infection should not be allowed to divert suspicion from empyema.

Where the organism present at surgery was identified, pneumococcus alone was the most frequent finding, but streptococcus and staphylococcus occurred alone and in various combinations with pneumococcus and each other. Staphylococcus was rare in older children and streptococcus was rare in younger (see Table V). In 5 cases no organism could be cultured; 2 of these ended fatally. In 2 of these sterile cases no antecedent infection was known, but both had fever. Seven out of 25 cases with staphylococcus present terminated fatally (28.0 per cent) while only 14 out of 94 in which pneumococcus was present did so (14.9 per cent).

TABLE V. INCIDENCE OF INFECTIVE ORGANISM

ORGANISM	UNDER 2 YEARS OF AGE	OVER 2 YEARS OF AGE
Staphylococcus only	10	4
Streptococcus only	0	4
Pneumococcus only	11	51
Pneumococcus and staphylococcus	4	4
Pneumococcus and streptococcus	2	19
Other mixed infections	2	8
Sterile	2	4
Unknown	0	8

The high mortality from staphylococcus infections is related to their frequency in younger patients. No pure staphylococcus cultures were obtained from patients over 3 years of age. This preponderance of staphylococcus infections in younger children has been noted in an editorial by Lindskog.[11] While the occurrence of staphylococcus infection amounted to 11.1 per cent of the cases when the organism was the only one present and an equal percentage when in combination with others, the variation from year to year was great. For example: in 1944, pure staphylococcus infections accounted for 41.6 per cent of the cases of empyema admitted; in 1939 they accounted for 7.1 per cent; in 1937, out of 15 cases there were none produced by staphylococcus. This serves to explain the wide variation in

incidence of this organism in various series of cases as collected by Riley.[12] While mortality is higher than in infections due to other organisms, patients with staphylococcus and streptococcus infections seem to recover faster as evidenced by a slightly shorter hospital stay.

We place little importance on the relative incidence of different causal organisms in short series or when expressed as over-all incidence in long series. The experience from year to year and hospital to hospital is too varied to permit prediction.

Thus, while age, year, sex, season, organism, and prior course of the disease all affect the incidence, mortality is relatively independent of all but age and the long-term cyclic changes. The result is that the mortality rate tends to become lower where incidence is highest. With Ladd and Swan,[13] "we feel that age is the single most important factor in relation to mortality."

Hospitalization for acute empyema is relatively long. Our survivors averaged 48.5 days, with a maximum of 212. Heuer[1] gives 39 days as his 1921-1930 average, and Penberthy and Benson[14] give 48.6 days for their Detroit series of 1926-1935. The latter included their fatal cases in the average which would tend to lower it. Of our patients who died, 9 did so within 10 days and only 2 died after the 49th day. Antibiotic therapy has not reduced hospital stay in our series; it has, in fact, slightly, though not significantly, prolonged it.

The chief complication of empyema in our series was bronchopneumonic fistula. It occurred in 10 patients, of whom one died. Where this complication was present, the mean hospital stay was 68 days, as compared with 46 days for all cases. Three were hospitalized for over 100 days.

Although we recognize that tension bullae may develop in young children with staphylococcic empyema, we saw this in only one of our cases.

Of the 22 deaths, 7 were attributed to heart failure, 5 to overwhelming septicemia, 1 to nephritis, and the rest were unspecified. All of these deaths occurred before 1947, which was about the time that the broad-spectrum antibiotics came into general use. In three patients death took place within 24 hours of admission, leaving little opportunity for any chemotherapy to have demonstrated an effect.

Seventy-eight of our patients received no chemotherapy. Thirteen died, resulting in a mortality rate of 16.7 per cent. Of 49 receiving chemotherapy (penicillin, sulfa compounds, or both), 9 died. Mortality was 18.4 per cent. The difference, apparently in favor of the untreated group, is of no statistical significance. In other words, the arrival of chemotherapy has not changed the rate of mortality from empyema; it has only decreased the incidence by controlling infection before empyema develops. Newer antibiotics, developed since 1947, have had no opportunity to demonstrate their value.

Adequate drainage remains the most important factor in treatment of those cases in which empyema has developed. Rib resection was done on 95 of the 111 patients who survived and on 7 of the 22 who died. Among the fatal cases, 11, or one-half, had aspiration without rib resection. Of these, 2 died on the first day and only 2 lived more than ten days. It is probable

that their condition did not warrant more radical surgery. One of us (B. L.) lately observed 5 patients with staphylococcal empyema (not included in this series) under 1 year of age who failed to respond to massive doses of the most recently developed antibiotics. Four of them responded well to thoracotomy and the fifth died because thoracotomy was done too late.

Fourteen patients survived with aspiration only and 8 of those aspirated had subsequent rib resection. In 2 cases rib resection and tracheotomy were performed; 1 lived and 1 died. One patient survived with drainage tube only. One bilateral empyema was successfully treated by rib resection on one side and drainage tube on the other. Treatment cannot rest upon chemotherapy. There is no substitute for drainage.

It is our policy to have a thoracocentesis tray with a small thoracotomy tube available at all times when the diagnosis of staphylococcic pneumonia in an infant is suggested. If pneumothorax develops, the tube should be inserted at once. Procrastination leads to dyspnea which may rapidly terminate in death. The associated use of tracheotomy and bronchoscopy to clear bronchial airways is imperative when signs of obstruction are present. It is well to keep in mind the possibility that a foreign body may be present in such cases of obstruction.[6]

Where thoracotomy tube drainage is inadequate, rib resection and oxygen drainage is indicated as strongly as in prechemotherapeutic days. Too great a delay in operation may result in fibrothorax with attendant decrease in pulmonary function and severe incapacitation. In none of the patients in this series have we had to resort to decortication, nor has fibrothorax developed in any who have been followed.

In the older age group, we feel that the restorative exercise of positive pressure breathing and blowing of balloons aid in the re-expansion of the involved lung. Apparently young children have great facility in dissolving the thick coating of exudate over their lungs and obtaining an adequately functioning pleura.

SUMMARY

One hundred and thirty-three consecutive cases of acute empyema in children under 14 years of age are presented. They occurred over a twenty-five-year period at the Henrietta Egleston Hospital for Children in Atlanta.

Incidence and mortality by age, sex, year, season, and causal organism are discussed. Incidence and mortality are highest for the youngest children and incidence is constantly higher in boys than in girls. Mortality rate bears little relation to incidence except with respect to age. Chemotherapy has reduced incidence to almost the vanishing point since 1947 but has had no effect upon mortality and morbidity once empyema has developed. Relative mortality from staphylococcus and pneumococcus varies so greatly from year to year that little predictive reliance can be placed upon it.

Adequate drainage including aspiration and open resection has not been replaced as the treatment of choice. Alert observation, special care, and constant attention are necessary in children under 2 years of age.

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Advertisement in the BRITISH MEDICAL JOURNAL
MARCH 20, 1858

CELIAC DISEASE: RESPONSE TO A GLUTEN-FREE DIET

Case Report

Stanley N. Graven, Captain, USAF (MC), and Edward J. Tomsovic, Major, MC, USA
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THE European literature contains many descriptions of the deleterious effect of wheat gluten upon patients with celiac disease. There are, however, no similar descriptions in the American literature. It is the purpose of this paper to present a case of celiac disease which resulted from an intolerance to wheat gluten. The subject of gluten-induced celiac disease is extensively reviewed in a recent monograph by Weijers and associates.[1]

CASE REPORT

Present Illness.—A 16-month-old Caucasian girl was admitted to the 5001st USAF Hospital, Fairbanks, Alaska, on Aug. 1, 1956, following 2 months of vomiting, associated with frequent large, pale, foul, bulky stools. She had lost 2.25 kilograms in weight.

Past History.—Pregnancy and delivery were unremarkable. Her birth weight was 3.26 kilograms. She was fed an evaporated milk formula with cereals and solid food in the diet by the third month. Growth and development were normal prior to the onset of illness. Immunizations were given at the

Table I. Laboratory Determinations

		8/1-10/56	8/12/56	8/21/56	12/3/56	
Hematology	Hb.	13.0			13.0	Gm. %
	Htct.	40	42	42	42	%
	RBC	5.0			5.2	Million
	MCH	26			25	
	MCV	80			81	
	MCHC	33			31	
	ESR	2				mm./hr.
	WBC	10,200	19,000		13,000	
	Neut.	34	37		32	%
	Eosin.	2	0		4	%
Urine	Alb.	Trace	Trace		Neg.	1-4 plus
	WBC's	8-10	Occ.		0	Cent./HPF
Blood chemistries	Tot. prot.	6.2		5.7		Gm. %
	Alb.	5.2		4.0		Gm. %
	Glob.	1.0		1.7		Gm. %
	Cholest.			235		mg. %
	Ca	10.6		9.2		mg. %
	P	4.0				mg. %
	FBS			70		mg. %
	Na			132		mEq./L.
	K			3.5		mEq./L.
	CO_2			15.6		mEq./L.
	Cl			125		mEq./L.
Stool	Culture	Neg. × 3	Neg.			
	O & P	Neg. × 3				
	Starch	Neg.		Neg.		
	Trypsin	1:640	Normal			
Duodenal aspirate	Culture	Neg.				
	O & P	Neg.				
	Amylase	34				Fister units
	Trypsin	1:640				

From the Madigan Army Hospital, Tacoma, Wash.

usual time. There were no significant past illnesses.

Family History.—A maternal first cousin had a diagnosis of celiac disease. The disease was described as an intolerance to dietary fat. The subsequent course of the relative's disease and treatment are not known. A paternal aunt has diabetes mellitus.

Physical Findings.—The child was a pale, lethargic, irritable, chronically ill girl who weighed 8.40 kilograms. The significant physical features were thin extremities, wasted buttocks, hollow cheeks, stringy hair, and protuberant abdomen. The abdomen had a firm, doughy consistency.

Course.—X-rays of the skull and chest were normal. An upper gastrointestinal series showed dilatation of the small bowel loops with segmentation. The results of the laboratory determinations, tolerance tests, and duodenal aspiration are noted in Tables I and II. Her bulky stools and vomiting improved on a diet containing skim milk, Casec, and fresh bananas. In spite of improvement in her symptoms, she failed to gain weight.

On the eleventh hospital day she was transferred to Madigan Army Hospital, Tacoma, Washington. On admission she weighed 8.05 kilograms. The physical findings were unchanged. Admission laboratory determinations are noted in Table I. After ingestion of a test dose of Lipiodol, iodine appeared in the urine in a dilution of 1:16. During the first 10 days in Madigan Army Hospital, numerous dietary regimens were tried in an attempt to control the vomiting and bulky stools which reappeared shortly after admission. All of the diets were uniformly unsuccessful. On the tenth hospital day oral feedings were discontinued. She was given whole blood and intravenous fluids for 36

TABLE II. STARCH, GLUCOSE, AND VITAMIN A TOLERANCE TESTS

DATE	TEST	TEST DOSE	TIMES AND VALUES					UNITS
	(Oral)		Fast	½ hr.	1 hr.	2 hr.	3 hr.	Blood Glucose
8/4/56	Starch tol.	100 mg. sol. starch	50	53	51	50	44	mg. %
8/6/56	Glucose tol.	50 mg. glucose	66	88	92	47	59	mg. %
9/11/56	Glucose tol.	50 mg. glucose	90	97	103	97	90	mg. %
			Fast	3 hr.	6 hr.	9 hr.		Blood vit. A
9/21/56	Vit. A tol.	5,000 U. vit. A/kg.	85	154	106	113		mcg. %

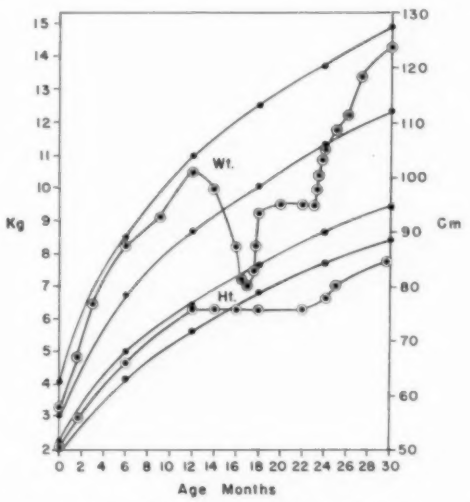


Fig. 1.—The effect of wheat on height and weight. Wheat was excluded from the diet from 16½ to 18 months of age and from 23 months on. (Original graph showed these periods as shaded areas.) The norms for height and weight are the 16th and 84th percentiles taken from the Iowa graph.

hours. At this time she weighed 7.01 kilograms. Her blood chemistries are noted in Table I.

diet, a small bowel x-ray series was performed. A second small bowel film was taken after wheat had been added to her diet for

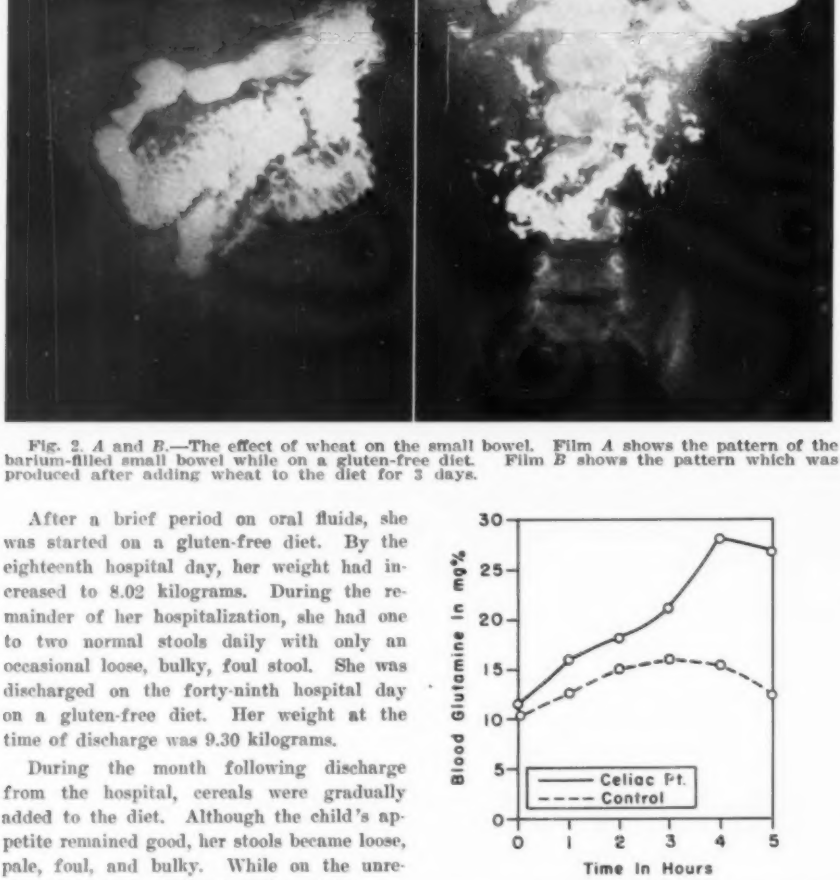


Fig. 2. *A* and *B*.—The effect of wheat on the small bowel. Film *A* shows the pattern of the barium-filled small bowel while on a gluten-free diet. Film *B* shows the pattern which was produced after adding wheat to the diet for 3 days.

After a brief period on oral fluids, she was started on a gluten-free diet. By the eighteenth hospital day, her weight had increased to 8.02 kilograms. During the remainder of her hospitalization, she had one to two normal stools daily with only an occasional loose, bulky, foul stool. She was discharged on the forty-ninth hospital day on a gluten-free diet. Her weight at the time of discharge was 9.30 kilograms.

During the month following discharge from the hospital, cereals were gradually added to the diet. Although the child's appetite remained good, her stools became loose, pale, foul, and bulky. While on the unrestricted diet, she failed to gain weight.

Four and one-half months later she was again started on a gluten-free diet. Within 4 days her stools returned to near normal. Her activity increased markedly with a concomitant improvement in her previously irritable nature. While she was on the gluten-free

Fig. 3.—Gliadin tolerance test. Gliadin is a fraction of wheat gluten. The test was performed by orally administering 350 mg. of gliadin per kg. body weight and determining hourly the concentration of blood glutamine. The patient who served as the control was an epileptic child of the same weight. Both children were fasted for eight hours prior to the test. Patients with celiac disease are reported to have a marked increase in blood glutamine following ingestion of gliadin.[4]

3 days (Fig. 2). Stool fat determinations before and after the introduction of the gluten-free diet are shown in Table III. A gliadin tolerance test performed while the child was on a gluten-free diet is shown in Fig. 3. The effect of the gluten-free diet on the child's growth is shown in Fig. 1. When last seen, on March 26, 1958, 19 months after the onset of her disease, she was a healthy-appearing 3-year-old girl (Fig. 4). Her stools were normal in frequency and consistency.

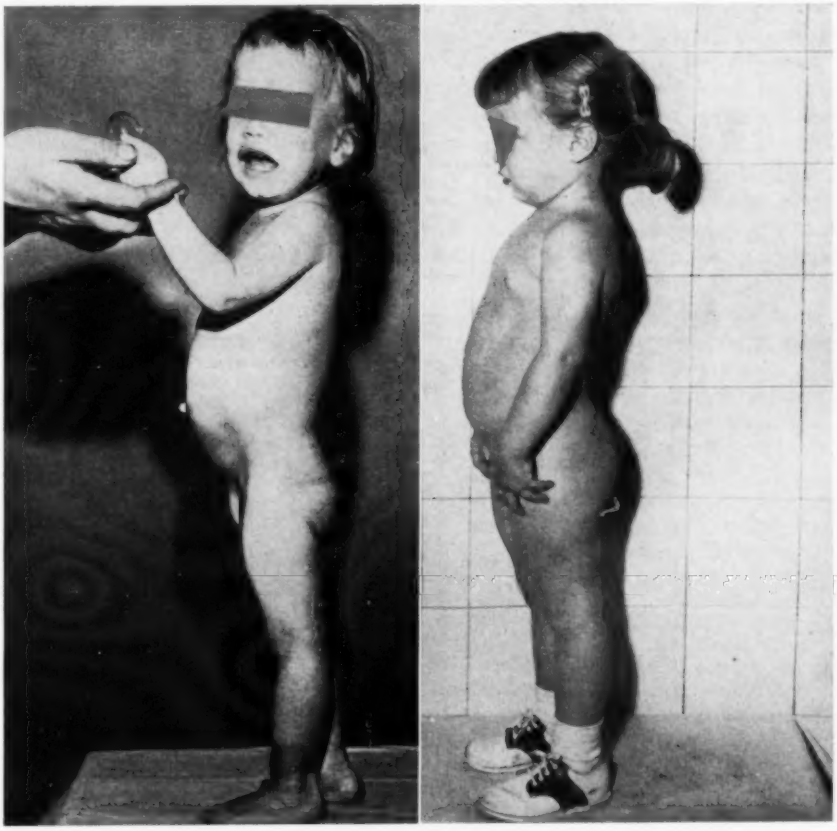
TABLE III. THE EFFECT OF WHEAT ON FAT EXCRETION

A†	B‡
29.5 per cent*	8.2 per cent
52.0 per cent	13.6 per cent
	5.5 per cent
	6.2 per cent
	13.5 per cent
	12.5 per cent

*Per cent of dry weight of the stool.

†The fat concentration on an unrestricted diet.

‡The decreased fat content while on a gluten-free diet.



A. *B.*

Fig. 4, *A* and *B*.—The effects of a gluten-free diet. In the first photograph, *A*, the child has been on a gluten-free diet for 18 days. The protuberant abdomen has decreased in size; however the wasted gluteal muscles and unhappy expression are still prominent. The second photograph, *B*, shows the child after 15 months on a gluten-free diet.

DISCUSSION

The age of onset, presenting symptoms, physical findings, stool characteristics, and early clinical course all fit the classic descriptions of celiac disease. The celiac crisis, which was part of this patient's course, was similar to the crises described in the older literature. The presence of celiac disease in the family history corresponds to the reported studies, in which 10 to 20 per cent of the cases show a family history of chronic gastrointestinal disorders.[2] The beneficial effect of the gluten-free diet on this patient's growth, stool fat content, and x-ray pattern of the small bowel is shown in Figs. 1 and 2 and Table III. It is important to note that between the periods on the gluten-free regimen the diet was calorically and nutritionally more than adequate. In spite of this the child failed to grow.

The marked decrease in stool fat noted after institution of the gluten-free diet is considered significant despite the fact that stool fat expressed as a percentage of the dry weight is not the most accurate measure of fat excretion.[3, 4]

SUMMARY

1. A case of celiac disease caused by ingestion of wheat gluten is presented. The response to a diet excluding wheat is illustrated.

2. The changes in the x-ray pattern of the small bowel and stool fat content before and after institution of the gluten-free diet are presented.

3. The results of a gliadin tolerance test are presented.

Mr. Quentin C. Belles performed the blood glutamine and stool fat determinations at the 6th Army Area Medical Laboratory, Fort Lewis, Washington. Photographs are by the Medical Illustration Section, Madigan Army Hospital.

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CEREBRAL ARTERIOVENOUS FISTULA PRODUCING CARDIAC FAILURE IN THE NEWBORN INFANT

Case Report and Review

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EXTRACARDIAC causes of congestive heart failure with marked cardiomegaly in the newborn period are relatively rare. Among the conditions which may give rise to an increased cardiac output with gross cardiac enlargement in the newborn period are: (1) patent ductus arteriosus,[1] (2) hemolytic anemias—such as erythroblastosis fetalis,[2] and (3) rarely, multiple telangiectasias of the cerebral vessels.[3]

In a recent report, Silverman and associates[4] described, as a fourth extracardiac cause of cardiomegaly with congestive failure in the newborn period, two newborn infants who had congenital arteriovenous fistulas of the cerebral vessels. Since this condition had not been described prior to Silverman's report, we feel that a third case, which we have recently encountered, might be of interest. This paper will present the clinical and autopsy findings in our case, and will briefly review the physiopathology involved.

CASE REPORT

A Negro male infant, weighing 3,629 grams, was delivered at term to an 18-year-old mother at the Louisville General Hospital. The delivery was uncomplicated. The infant was apneic for five minutes following birth, but responded well to resuscitation, and was transferred to the nursery for newborn infants.

Physical examination revealed a well-developed, active infant who was in no apparent distress, but whose head appeared disproportionately large. The occipitofrontal circumference measured 39 cm.; the anterior fontanel was flat and measured 3 by 3 cm. There was no evidence of distention of the vessels of the face or scalp; no tumor masses were noticed; and there was no exophthalmos. The head did not transilluminate light. Chest circumference at the nipple line was 33 cm., and the baby's length was 52 cm. The cardiorespiratory systems did not appear remarkable.

Course.—At 51 hours of age the infant was noted to be lethargic and breathing rapidly. He refused his feedings. There was no cyanosis, but flaring of the alae nasae, subcostal retractions, and a respiratory rate of 75 per minute were present. The lung fields were clear to auscultation. The heart rate was 160 per minute with a gallop rhythm and the heart was enlarged to percussion. No murmurs were detected. The neck veins were distended and the liver was palpable 4 cm. below the right costal margin.

A portable chest film showed a tremendously enlarged heart with no evidence of pneumonia or collapse of the lungs (Fig. 1). An electrocardiogram revealed a sinus tachycardia

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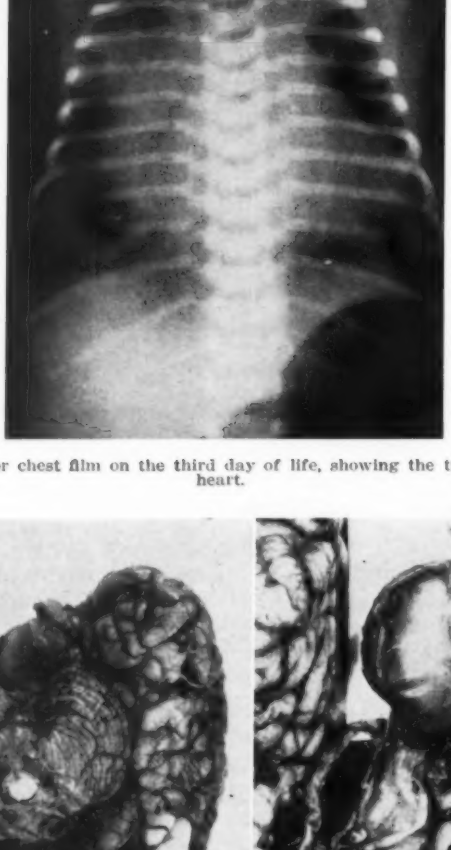

Fig. 1.—Posteroanterior chest film on the third day of life, showing the tremendously enlarged heart.

Fig. 2.—Large aneurysmal sac in the region where the vein of Galen joins the straight sinus, as seen from below.

Fig. 3.—Cerebellum reflected to demonstrate the large aneurysmal sac, the unusually large posterior cerebral and superior cerebellar arteries on the right (arising from a dilated basilar artery), and the approximately normal-sized vessels on the left.

and S-T segment changes suggestive of coronary artery insufficiency.

The baby was placed in moist oxygen and digitalized over a four-hour period with 0.045 mg. per kilogram of body weight of Digitaline Nativelle. The infant's condition gradually deteriorated and he expired on the fourth day of life, at 83 hours of age.

Necropsy Findings.—"In the region where the vein of Galen joins the straight sinus there is a large aneurysmal dilatation which is dark blue and quite firm to palpation. This is ovoid measuring about 2 cm. in greatest dimension. On close inspection it is found that this aneurysmal sac receives vessels from both the internal cerebal veins and from both posterior cerebral and superior cerebellar arteries. Most of these tributary vessels of the aneurysmal sac appear to be thrombosed. Examination of the vessels at the base of the brain show a dilated and apparently thrombosed basilar artery which gives rise to unusually large posterior cerebral and superior cerebellar arteries on the right side, but approximately normal sized vessels on the left. A posterior communicating vessel is demonstrated on the left side but not on the right. Apparently the latter had been previously transected. The other vessels comprising the circle of Willis do not show any remarkable changes. The brain itself weighs 460 grams and shows no other remarkable external changes."

The significant gross findings were: (1) cardiac hypertrophy and dilatation; (2) acute passive congestion of lung with alveolar hemorrhage and edema; (3) bilateral hydrothorax; and (4) ascites.

DISCUSSION

The typical congenital cerebral arteriovenous aneurysm as described by Ray,[5] Cushing and Bailey,[6] Ford,[7] Hamby,[8] and others, consists basically of three parts: (1) the artery which supplies the lesion, (2) a tangled mass of dilated veins, and, variably, (3) an interposed bed of dilated vessels which occupy the position of the capillaries and in which there are many arteriovenous communications. The blood flow is from the artery directly to the vein, bypassing any capillary network. The lesion may be circumscribed, or very extensive, and there is frequently an audible bruit and often a palpable thrill present.

Location.—While in the majority of cases reviewed[5-11] the anomalous formation has involved the middle cerebral artery, the malformation may occur in arteries anywhere in the brain. The posterior cerebral artery is the second most frequent location of involvement.

Clinical Picture.—The usual clinical picture described[5-8] is that of a lesion which manifests itself in adolescence or early adult life by signs of increased intracranial pressure, headaches, epileptiform seizures, focal neurologic signs, and, frequently, increased extracranial vascularity with dilatation of the veins of the scalp and face and of the retina, and, on occasion, exophthalmos.

While congenital cerebral arteriovenous aneurysms are a not infrequent occurrence, symptoms in infancy or childhood are rather uncommon. Cushing and Bailey,[6] in 1928, stated that to their knowledge the lesion had not been observed in infancy. We have found reference[4, 5, 9, 10, 11] to only a few cases with onset of symptoms in infancy. Of these, only four appear to have had any manifestation of the cardiovascular complications of an arteriovenous fistula.

Silverman and associates[4] have described two newborn infants who died

shortly after birth with gross cardiomegaly and congestive failure. At autopsy, communications of the middle and posterior cerebral arteries and the superior sagittal sinus were found in one, and of the middle cerebral artery and the sigmoid sinus in the other. The heart in both instances was enlarged, but was otherwise normal.

Jaeger and Forbes[11] have reported a 4½-year-old boy who at birth was thought to have an abnormally large head. At 8 months of age he began having episodes of epistaxis and was first noted to have dilatation of the scalp and face veins, as well as an increased area of cardiac dullness. By 15 months of age his head was described as "large," and shortly thereafter a bruit became audible over the neck. Despite ligation of the left carotid artery, the patient died following a convulsion and at postmortem examination was found to have bilateral arteriovenous communications of the posterior and middle cerebral arteries. The heart was enlarged but otherwise normal.

Ray[5] reports a 4-year-old boy whose first symptoms were manifest at 2½ years of age with left hemiparesis, an enlarged head, dilated veins of the head, scalp, and of the vessels of the retina, as well as an enlarged heart. There was a bruit audible over the entire head. Four weeks following ligation of the common carotid arteries, the heart size was definitely decreased. Death, however, occurred following a second operation, and at postmortem the child was found to have an arteriovenous fistula involving the right middle cerebral artery and the sagittal sinus. Apart from slight dilatation and hypertrophy, the heart was usual in appearance.

Influence on Cardiovascular System.—The effects of an arteriovenous fistula upon the cardiovascular system may be far reaching. This is a principle that has been well established by the experience with arteriovenous fistulas throughout the body in man, and by the experimental production of fistulas in lower animals. Holman[15] points out that an arteriovenous fistula produces short-circuiting of a volume of blood, and due to the reduced peripheral resistance, introduces a degree of inefficiency into the circulatory system. The resulting changes in the cardiovascular system are dependent on the volume of blood shunted, which is dependent entirely upon the size of the fistula.

The observations of Holman,[13-15] Warren and Elkin,[16, 17] Epstein and associates,[18] Jounart and co-workers,[19] and others, have confirmed that arteriovenous fistulas are frequently associated with (1) an increased cardiac output, (2) dilatation of the heart, (3) a lowering of the diastolic arterial pressure, and (4) occasional evidence of myocardial damage on the electrocardiogram. Gregg and Sabiston[20] state that in a peripheral arteriovenous fistula, "there is an increase in the cardiac output, cardiac work, and cardiac oxygen usage. Concurrently, the vascular inflow of the left coronary increases while its vascular resistance decreases." Most authors have pointed out that frank congestive failure could occur either early or late in the condition.

Jounart and co-workers,[19] working with unanesthetized dogs, found that sudden release of compression of an experimental femoral arteriovenous fistula led to a passive drop in the systolic and diastolic arterial pressure

as a result of the lowered arterial resistance. This was followed by a two-stage adaptation reaction: the first was mediated by the carotid sinus reflex and consisted of tachycardia with more complete emptying of the ventricles; the second stage was characterized by systemic vasoconstriction and a rise in cardiac output. As the systemic pressure rose, the tachycardia slowed until an equilibrium was reached. Similar observations have been made by Epstein and associates,[18] studying traumatic arteriovenous fistulas in men by cardiac catheterization.

It is suggested then that a large arteriovenous fistula produces a lowered peripheral resistance, which in turn leads to an increase in cardiac output, perhaps as a result of three factors[4, 18, 19]: (1) a carotid sinus reflex producing an increased heart rate, (2) a decrease in the pressure in the aorta against which the left ventricle must work, and (3) an increase in inflow of blood to the right heart, resulting in increased distention of the ventricles during diastole. This increase in cardiac output, cardiac work, and cardiac oxygen consumption may result in dilatation of the heart, and on occasion in cardiac failure.

That the cerebral arteriovenous fistula may result in effects on the cardiovascular system similar to effects of arteriovenous fistulas elsewhere in the body, has been confirmed by the observations of Shenkin and associates.[21] Ray,[5] however, points out that on the whole the effects of an arteriovenous fistula of the cerebral vascular system are usually less pronounced than lesions elsewhere. This he attributes to the facts that (1) the middle cerebral artery, which is the cerebral artery most frequently involved, is much smaller than those frequently involved elsewhere in the body, and (2) the malformations of many small vessels between the cerebral artery and the cerebral veins minimize the effect of the fistula.

In any event, the symptoms of cerebral arteriovenous aneurysms are rare in infancy, and the cardiovascular complications even more so. Nevertheless, cerebral arteriovenous fistula as the cause of gross cardiomegaly and cardiac failure in the newborn period should be borne in mind. If thought of, such a diagnosis could conceivably be made ante mortem, as an audible bruit would most likely be present. In none of the three cases reported to date, however, has the diagnosis been made prior to death.

SUMMARY

In the newborn infant, extracardiac causes of congestive failure with associated marked cardiomegaly include: (1) patent ductus arteriosus, (2) hemolytic anemias, (3) multiple telangiectasias of the cerebral vessels, and (4) cerebral arteriovenous aneurysm.

The clinical and pathologic findings are presented of a newborn infant who had cardiomegaly, cardiac failure, and at postmortem examination was found to have a cerebral arteriovenous fistula.

Congenital cerebral arteriovenous aneurysms most frequently involve the middle cerebral artery.

The usual clinical picture is described, and cases with cardiovascular complications in infancy are listed.

As a result of lowered peripheral resistance, arteriovenous fistulas are frequently associated with (1) an increased cardiac output, (2) cardiac

dilatation, (3) lowering of the diastolic pressure, (4) occasional evidence of myocardial damage on the electrocardiogram, and (5) cardiac failure. The mechanisms for these findings are discussed briefly.

While cerebral arteriovenous fistulas are a very rare cause of extracardiac heart failure and gross cardiomegaly in the newborn period, it is pointed out that the possibility should be kept in mind.

We are indebted to Dr. William M. Christophersen of the University of Louisville School of Medicine, Chairman of the Department of Pathology, for the necropsy findings.

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METHEMOGLOBINEMIA ASSOCIATED WITH INTESTINAL STRANGULATION OBSTRUCTION IN THE NEWBORN INFANT

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CYANOSIS in premature and newborn infants during the first 3 months of life may occasionally be due to an altered blood pigment rather than to a defect in oxygen transport. In recent years the medical profession has been alerted to secondary methemoglobinemia states caused by aniline derivatives and nitro compounds which gain entrance to the body through the skin, lungs, or gastrointestinal tract.[1, 2, 12] Certain of the older drugs, including acetanilid and the sulfonamides, had such an effect. Methemoglobinemic outbreaks have followed the ingestion of nitrate-containing well-water[5, 11] or skin contact with laundry marking ink[2] in the nursery. Acquired extracellular or plasma methemoglobinemia is associated with paroxysmal hemoglobinuria, sepsis due to anaerobic organisms, and hemolytic icterus.[1] In these instances, hemoglobin dissolved in the plasma can be oxidized to methemoglobin.

The possibility of concomitant methemoglobinemia and intestinal obstruction has not been widely discussed. Cohn,[3] while searching for abnormal blood pigments in the ascitic fluid associated with intestinal strangulation obstruction, reported the presence of methemoglobin in the samples of two patients in his series. One patient, a 74-year-old white woman, was treated for a closed-loop strangulation obstruction secondary to an inguinal hernia. A second patient, who developed mesenteric thrombosis, was found to have methemoglobin pigment in the dark serosanguineous ascitic fluid. No mention of methemoglobin pigment was made on the peritoneal fluid analysis of six other patients with relative strangulation obstruction. Although no young infants were studied in Cohn's series, it is widely accepted that infants under 12 weeks of age have an intestinal bacterial flora which produces nitrite especially well,[4] and their hemoglobin is particularly susceptible to oxidation.[2] The following case is presented as an apparent methemoglobinemia which followed surgery for strangulated inguinal hernia in a 4-week-old infant.

CASE REPORT

A 1-month-old white boy was admitted to the hospital because of vomiting, a scrotal swelling, loss of appetite, and cessation of bowel movements. The mother stated on admission that the baby was born at full term and that he was normal in every way except for a moderate enlargement of the right scrotum which was believed to represent a hydrocele. The

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infant's development was satisfactory until two days prior to admission when the right scrotal mass became tense and discolored. When the mother touched the bulging area, the baby appeared to experience distress. He continued to take milk feedings and did not vomit. On the day prior to admission one bowel movement was passed and the baby seemed quite irritable. He vomited his morning feeding. The bowel movement represented several hard, round stools with dark red blood on the surface. Little formula was taken and each subsequent feeding was vomited. Emergency hospitalization was arranged immediately after a medical examination.

On examination the temperature was normal, the pulse rate 120 and regular, and the respiratory rate 28 and regular. The baby appeared to be well developed. The skin was dry. There was no sign of acute distress; the baby was quite somnolent. The ears, nose, and throat looked healthy. There was no significant lymphadenopathy. The lungs expanded symmetrically and were clear to percussion and auscultation. The abdomen was moderately distended but not tender. The liver and spleen were not palpable. There were no scars. A swollen, tender, nonreducible mass was present in the right scrotum which gave a dark discoloration to the area. Hemoglobin was 14 Gm. and the white count showed 14,000 cells. Urine was not obtainable because of dehydration. A scout film of the abdomen revealed numerous loops of small bowel measuring 1 to 1.5 cm. and they took a step-ladder position across the upper abdomen. No dilated loops were seen in the lower quadrant, possibly because of ascitic fluid.

Hydration was achieved with a mixture of 50 ml. of 5 per cent glucose in water and 50 ml. of normal saline. The baby was then taken to the operating room for correction of the strangulated right inguinal hernia. At operation a closed-loop strangulation obstruction was found and the extra-abdominal, peritoneal sac contained reddish-black, noncoagulable, nonodorous fluid. The loop of small bowel had an edematous, dusky color which reverted to a more normal appearance with enlargement of the tight internal ring. The mesentery was edematous and discolored with petechial hemorrhages. The peritoneal cavity contained a large amount of cloudy, yellow serous fluid. Approximately fifteen minutes after the closed loop was liberated, the anesthesiologist noticed cyanosis and he aspirated the tracheobronchial tree. No fluid was obtained. He then aspirated the nasogastric tube without benefit. After completion of the hernial repair, the infant was sent to the recovery room and he was given nasal oxygen because of the dusky color. During the next fifteen minutes the baby became increasingly cyanotic despite good aeration of the lungs. A bronchoscope was passed; however, the tracheobronchial tree was found to be clear. Slight improvement in the slate-colored appearance occurred in the next hour. The blood smear appeared to be chocolate-colored. When compared with a control sample of normal blood, it did not change color with agitation on a glass slide in a pure oxygen atmosphere. Intravenous methylene blue (0.2 mg. per kilogram) was given. Complete clinical reversion to a healthy, normal color took place within ten minutes. No relapse to the cyanotic state occurred. The postoperative course was otherwise uncomplicated; and the infant was discharged from the hospital on the fifth day. Spectrophotometric studies at the age of 6 weeks showed no evidence of a primary or familial methemoglobin trait. The baby's subsequent development has been normal.

DISCUSSION

Methemoglobin is a true oxide of hemoglobin containing trivalent iron instead of bivalent iron. One and a half grams per 100 ml. of blood are enough to give the skin a slate-blue

cast. Normally there is some oxidation of hemoglobin to methemoglobin, but the amount is small and the process is reversible during the oxidation of glucose and lactate under the influence of the coenzyme systems.[2] Infants appear to be especially susceptible since their intestinal flora[4] (*Escherichia coli* and *A. aerogenes*) produce nitrites well in an acid medium. The newborn hemoglobin is prone to undergo oxidation more readily.[2] Nemir, Hawthorne, and Drabkin[6] showed that incubation of whole blood with hemolytic *Clostridium welchii* in vitro was followed by a rapid change to methemoglobin.[6] Studies on patients with congenital methemoglobinemia show low ascorbic acid levels[7, 8] and a deficiency of coenzyme I.[10] Vitamin C is presumably linked with the reduction of methemoglobin in the red cell. The influence of nitrite on hemoglobin is variable. The nature of the reaction will vary[9] with (1) the amount of nitrite, (2) the pH of the medium, (3) the presence or absence of other oxidizing or reducing agents, (4) intact enzyme systems.[1]

While the etiology of the apparent severe methemoglobinemia in this reported infant is not clear, many factors must be considered. The preoperative skin color was not good, but there was no clinical suspicion of an altered blood pigment state. The cyanosis did not seem to follow immediately after the administration of the half normal saline and 2½ per cent glucose solution by vein. Rather, the progressive cyanosis began shortly after releasing the obstructed loop of small intestine. The dusky color of the involved bowel with marked edema and hemorrhagic injection of the mesentery and the dark reddish-black fluid on the closed, peritoneal, inguinal sac would suggest that the obstructive process had been present for some time. Ample opportunity for bacterial growth, intraluminal hemorrhage, hemolysis, and change of nitrate to nitrite could have taken place. The existing dehydration acidosis would have favored the tendency toward the oxidation of hemoglobin to methemoglobin. With the release of the trapped intestinal content, gradual absorption from adjacent normal mucosa could have occurred. All of these factors, together with a possible deficiency of vitamin C and the neonatal susceptibility to methemoglobinemia, might have played a role in this instance.

Subsequent progress of the infant has been normal. Convalescence following surgery was excellent. Examination at the age of 18 months (June, 1958) revealed normal physical and mental growth and development. There has been no recurrence of untoward gastrointestinal symptoms. A mild hypochromic anemia at the age of 2 months responded well to routine hematinic therapy. The right testicle appears to be moderately atrophic.

CONCLUSIONS AND SUMMARY

1. A case of methemoglobinemia associated with intestinal obstruction in a newborn infant is presented.

2. The various factors which may bear a relationship to the altered blood pigment in this infant are discussed.

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The Importance of Physical Exercise (apropos—the current President's Committee)

How many of the good qualities of Englishmen do we owe to our love of games and field sports! How many of the splendid empires we have founded in every quarter of the globe have had their root and spring in the tussles at Eton, the annual boat-races on the Thames, or the cricket matches on the thousand greens and heaths throughout broad England! The dominant race of the world—that race which has already seized upon every unoccupied corner of the world, and mastered the most thickly peopled—is dominant because it is great and masculine, because its tastes and habits lead to self-reliance, and because its breeding leads to the development of endurance, courage and pluck. We have been so accustomed to the habits that foster these noble qualities that we do not, we believe, thoroughly appreciate them—nay, we do not perceive that a current of opinion has set in among a certain small minority amongst us which, if carried to its full extent, would do much to unman the Englishman and to degrade his physical nature to the continental standard. We have only to look across the Atlantic to see how easily the healthy, jolly, muscular Englishman can degenerate into the sallow, dyspeptic, lanthern-jawed Yankee. No doubt the influence of climate has very much to do with this falling-off of the race; at the same time, it cannot be denied that a very large share of this deteriorating process is due to the false habits of our descendants themselves. A New England farmer is ruddy enough and stout enough, but your citizen of New York is so different a creature, that we scarcely can recognise him as of the same race.

From an Editorial in the BRITISH MEDICAL JOURNAL FOR 1858

COPROLITHS (CALCIFIED APPENDICEAL CALCULI) IN CHILDREN

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THE presence of a calcified appendiceal calculus in a young child who has acute abdominal symptoms is usually an indication for immediate surgery. To emphasize the importance of these concretions, a brief discussion and a case report are presented.

Coprolith, a word of Greek derivation, means dung-stone.[1] These were at one time believed to be quite rare. Lowenberg[2] found only 17 reported cases in 1949 and concluded that the condition was uncommon. Radiologists, however, see many cases of calcified enteroliths in the appendix. In a recent review, radiologists Berg and Berg[1] found 130 previously reported cases and added reports of 42 cases seen in their clinic over a five-year period.

Although there is no unanimity of opinion about the mechanism of coprolith formation, it is probable that a bolus of fecal material becomes lodged in the appendix, and calcium salts from the mucous glands in the crypts of Lieberkühn are deposited upon the concretion.[2]

The extreme importance of calcified appendiceal stones deserves emphasis. As Laforet and associates[3] have stated, "The condition is neither as uncommon nor as unimportant as is customarily assumed and failure to evaluate properly may result in disastrous temporizing." *When a radiopaque appendiceal coprolith is found in a child with abdominal symptoms, and other abnormalities have been ruled out, immediate surgery should be performed.*

From a number of well-written papers,[1-4] a number of lessons may be learned and some definite conclusions drawn. Not infrequently symptoms of appendicitis or abdominal symptoms have been minimal, yet if the radiologist's findings of the coproliths have been ignored, the appendix has ruptured in a high percentage of cases. In the patients seen by Berg and Berg,[1] findings other than coproliths were insufficient to justify a diagnosis of appendicitis in 50 per cent. Yet the combination of mild abdominal symptoms plus the presence of a coprolith was a definite indication for immediate surgery. They found that 90 per cent of such patients had acute appendicitis, and in 48 per cent the appendix was gangrenous or perforated.

When the patient is asymptomatic but has a demonstrable appendiceal calculus, should surgery be performed? In a young child, probably so. Laforet, Greenler, and O'Brien at Cambridge, Massachusetts, City Hospital point out that acute appendicitis with appendiceal concretion is generally of a particularly virulent type, that fecaliths are a common cause of appendiceal obstruction, and that the deposition of calcium salts is an indication of past or present inflammation. These authors therefore feel that an appendectomy is usually indicated. Radiologists Berg and Berg[1] agree with most other authors who recommend an *immediate appendectomy whenever a coprolith is found,* with the possible exception of a few symptom-free older patients.

The physician frequently sees children with vague abdominal pain, but seldom takes an x-ray of the abdomen because of the infrequency of the presence of abnormality, because of the cost to the patient, or because he wishes to minimize x-ray exposure. A coprolith or some other abnormality may be found in the child with vague abdominal pain and therefore a "flat plate" is justified.

The differential diagnosis of radiopaque intra-abdominal opacities includes ureteral or renal calculus, gallbladder stones, phleboliths, calcified mesenteric lymph nodes, and radiopaque medications. Enteric-coated tablets, antacids, and diuretics are said to cast the densest shadows.[1]

CASE REPORT

A 23-month-old white boy became ill 48 hours before being seen in a physician's office. During this period he had a slight temperature elevation (100° to 101° F. rectally), ate poorly, and seemed abnormally sleepy but could be roused. He vomited several times. A few hours before being seen, the child complained of pain in his right side. This was not sharply localized and the mother was uncertain of the location, duration, or intensity.

One week or so previously the boy was believed to have swallowed a plastic button which had not been found in the bowel movements.

A complete physical examination was done. The child was very difficult to examine and cried constantly. He was pale and appeared acutely ill. A mild left otitis media was present. No abnormalities of the eyes, nose, mouth, throat, neck, thorax and lung fields, back, or extremities were found. There was slight nonlocalized tenderness of the right lower quadrant of the abdomen, but no other definite abnormality. There was no rebound tenderness. A few bowel sounds were heard. No rigidity was present. No areas of tenderness were found on rectal examination.

A urinalysis was normal. A white blood count was 30,000 cells per cubic millimeter, with 80 per cent segmented forms, 8 per cent stab cells, and 12 per cent mature lymphocytes. Hemoglobin was 12.1 Gm. per 100 c.c.

Immediate surgery was deferred but the infant was admitted to the hospital for careful observation. Throat cultures were made. The child was started on a broad-spectrum antibiotic, and fluids were administered. During the next 12 hours (overnight) the boy seemed definitely to improve. He continued to run a temperature of 101° to 102° F. rectally. Re-examination 12 hours after admission revealed that the abdomen was quite soft and no tenderness, rigidity, or abnormal mass could be felt. A white blood count was taken. The total white count was 21,600 cells per cubic millimeter, with 77 per cent segmented forms, 10 per cent stab forms, 13 per cent lymphocytes, and 7 per cent eosinophils. The child seemed to have no pain, did not vomit, but refused food in the next 7 hours. On the afternoon of the day following admission, the boy suddenly seemed to become much worse. His temperature went to 104° F. rectally and he cried with abdominal discomfort. The white blood count increased to 26,600 cells per cubic millimeter, with 65 per cent segmented forms, 27 per cent stab cells, and 7 per cent lymphocytes. X-ray studies were done. A chest x-ray was normal. A scout film of the abdomen showed the presence in the right lower quadrant of an oblong area of smooth calcification measuring 1 cm. in width and 1.5 cm. in length, diagnosed by Dr. Robert Zaeh, radiologist, as a calcified appendiceal calculus or coprolith (Fig. 1).

The child was taken immediately to surgery. A right lower quadrant incision was made. As soon as the peritoneum was opened, frank pus was found. When the cecum was brought up into the wound, the surgeon noted that the appendix was ruptured. Three centimeters from the base of the 8 cm. long appendix and just proximal to the rupture, was a calcified fecalith completely obstructing the lumen of the appendix.

The child did well postoperatively and was discharged from the hospital after 2½ weeks. An uneventful recovery ensued. The supposedly ingested button never did appear and must be classified as a plastic "red herring."

Fig. 1.—Coprolith (calcified appendiceal calculus) in right lower quadrant.

Several important points are well illustrated by this case. The great need for immediate surgery was apparent. Even though the abdominal findings were somewhat equivocal, the x-ray finding of a coprolith proved to be very important. Finally, as might well have been anticipated, the appendix was found to be ruptured.

SUMMARY

Radiopaque appendiceal calculi (coproliths) are of great importance when found in children. They are not extremely uncommon. When a coprolith is found in a child who has abdominal symptoms, surgery is indicated. In asymptomatic children, surgery, in our opinion, is usually indicated. An illustrative case is presented.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

THIS 6-month-old white female infant was born to a gravida ii, para 0, 24-year-old woman whose pregnancy was uncomplicated. The infant was active in utero from the fourth to the ninth month of gestation. The delivery of the infant was without difficulty and the birth weight was 7 pounds and 13 ounces.

Immediately after the birth, the infant was placed in an Isolette and the day after birth a lumbar puncture was performed, which produced a few leukocytes and erythrocytes. At this time a diagnosis of a cerebrovascular accident was made. On the third day of life, because of an inability to suck vigorously, gavage feedings were started. These feedings were marked by numerous cyanotic spells. At this time, an intermittent tremor of all extremities was noted; this continued for the first 3 months of life. At 4 days of age the infant developed a fever of 104° F. and was placed on antibiotics, which were continued until discharge from the hospital of her birth at 3 weeks of age.

At home, the patient did not improve, was difficult to awaken for feedings, and showed no ability or desire to suck. She was fed with an eye-dropper and then gradually weaned to soft baby foods, taken from a cup. At 2 months of age she responded to affection and was alert, but seldom moved her extremities. At the time of admission to this hospital, the infant was beginning to hold up her head.

There was no family history of muscular weakness or neurological disorder.

On admission to The Children's Medical Center, the infant was alert, slightly apprehensive, pale and obese, but in no distress. The vital signs were: temperature 98.9° F., systolic blood pressure 60 mm. Hg, respirations 20, and pulse 120 per minute. The head measured 43 cm. in circumference and was wide in the bio-occipital diameter. The chest was symmetrical but flattened in the anteroposterior diameter, with marked depression of the sternum. Breathing was diaphragmatic in character with little intercostal movement, so that the "chest collapsed on inspiration." The cry was weak. A diffuse symmetrical weakness was present, more marked in the trunk and proximal limb muscles than in the peripheral muscles. The cranial nerve functions and sensation were normal throughout. Of the

deep tendon reflexes, only the ankle jerks could be elicited.

The initial blood studies included a hemoglobin of 14.0 Gm. per cent, a leukocyte level of 20.0 thousand per cubic millimeter, with a differential count on smear of polymorphonuclear cells 42, band forms 18, and lymphocytes 40 per cent. The urine was cloudy, with a pH of 5.5, sugar 0, albumin 30 mg. per cent, and a sediment containing 1 to 2 leukocytes per high-power field. The opening spinal fluid pressure was 165, the closing 95 cm. of water; the sugar, albumin, and cell count were normal. An electroencephalogram was normal.

Because of the infant's leukocytosis, she was placed on sulfisoxazole 0.5 Gm. twice a day. On the third hospital day, a repeat leukocyte count was 8.6 thousand per cubic millimeter; at this time a muscle biopsy was performed without complication. For the first 6 hospital days, the infant fared well, but on the seventh day she suddenly became cyanotic after feeding. Auscultation of the chest revealed râles at both lung apices. A diagnosis of aspiration pneumonia was made, which was confirmed by roentgen examination. The infant's trachea was suctioned; she was given oxygen, intramuscular penicillin and streptomycin. For the next 24 hours her condition remained stable with a temperature of 102° to 104° F., pulse 144, and respirations 36 per minute. She continued to take fluids by mouth, but early in the afternoon of the eighth hospital day she suddenly expired.

DISCUSSION

DR. DEREK DENNY-BROWN.*—I think that we can take it, from the details given, that there was no factor of importance to her fundamental disease relating to the manner of delivery of this infant. Immediately after birth the child was placed in an Isolette, probably because of some general weakness or breathing difficulty, for at 2 days of age a lumbar puncture was performed. It was found that a few white cells and a few red cells were present in the fluid, and a diagnosis of cerebrovascular accident was considered.

We are also told that an intermittent tremor of all extremities was first noted at 3 days of age, and this persisted for the first 3 months of life. I shall assume that the tremor was some type of weak attempt at normal limb movement. Development of natural movements of the limbs and body was evidently greatly delayed.

On admission to the hospital the chest "collapsed on inspiration." This pronounced indrawing of the ribs, and particularly of the sternum, is common with intercostal weakness or paralysis, and this was presumably the situation with this child. There was a diffuse symmetrical weakness more marked in the trunk, and more in proximal than in the peripheral muscles. Presumably the child was moving the hands and toes, but showed difficulty in elevating any limb.

Laboratory work on admission failed to reveal anything of importance. There was a mildly elevated white count, no findings of significance in the urine or spinal fluid. We can say that no inflammatory process was reflected in the cerebrospinal fluid, but perhaps more important, in view of the general weakness, there was no evidence of block of spinal fluid, such as might be found with compression of

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the spinal cord or obstruction at a higher level.

The story, then, is that of a 7½-month-old female infant who, at the time of death, had some type of diffuse muscular weakness. Since birth she had been unable to suck, had great intercostal and proximal muscular weakness, great delay in holding up the head, and inability to sit up. She was alert, showed affection, anxiety, and had a reasonable amount of vision and cerebration for her age. The muscles appeared to have been flabby, but only by inference because no spasticity is described. The ankle jerks and some sensation to pinprick were present. There is, therefore, no reason to suspect the presence of compression or destruction of the spinal cord or of the brain.

Attention is directed to the condition of the muscles. It is seldom possible to gain much information from palpating the muscles in a very young child, or even to ascertain the presence of atrophy, except in a most approximate manner, owing to the thick panniculus. We can only note that the muscular weakness was symmetrical, and greater in the proximal muscles and body. There was early involvement of the intercostal muscles, for although the child could not suck, she could use the lips for expression in smiling and other movement.

This condition has the general appearance of amyotonia congenita or Oppenheim's disease, which causes weak, flabby, atonic muscles, usually with no tendon reflexes, dating from earliest infancy. Brandt,[1] a Danish physician, has shown that amyotonia congenita is a symptom complex caused by any of several diseases; it is not by itself a pathological entity. There are at least four possibilities. The first is Werdnig-Hoffmann's disease—a progressive loss of motor neurones of the same nature that we recognize in the adult as amyotrophic lateral sclerosis. This is a progressive "neural" or nerve cell atrophy, beginning in earliest infancy. About 50 per cent of the patients with Werdnig-Hoffmann's disease show weakness at birth. The weakness usually becomes severe in the next 4 to 6 months. The limbs become wasted in all parts, and the reflexes are progressively lost. The course of the disease varies greatly but about 50 per cent of the patients fail to survive the first year. Another 25 per cent succumb before the age of 4, and very few survive beyond the age of 10 years. The course, just as in amyotrophic lateral sclerosis in the adult, is fairly steady progression of disability which results in very great atrophy of muscle before death. In the early stages it seldom involves the proximal muscles severely, but it involves all the muscles in time. Werdnig-Hoffmann's disease is listed in most textbooks as the usual cause of amyotonia congenita. That is because the children who die in the first year in this syndrome are usually found to be suffering from Werdnig-Hoffmann's disease, but it would be a great mistake to suppose that all amyotonia congenita is the same as Werdnig-Hoffmann's disease.

A second, far more uncommon condition found at autopsy in such infants is a type of progressive muscular dystrophy, with intact nerve cells. This infantile type of muscular dystrophy is not one of the classical types of dystrophy, such as pseudohypertrophic muscular dystrophy, Landouzy-Déjerine's, or Erb's juvenile dystrophy. It is already present at birth and is

more rapidly progressive than the classical types, though death in the first year of life is uncommon. Pseudohypertrophic muscular dystrophy is the most severe of the classical dystrophies. It begins in earliest childhood, but its manifestation is usually not noted until the second or third year, and quite often at four or five, when the child begins to present the characteristic waddling gait and enlarged calves. Thus a baby that is *born* with weak muscles is not likely to be suffering from that particular variety of classical muscular disease.

Though children born with amyotonia, who come to autopsy, are commonly suffering from Werdnig-Hoffmann's disease, and a few occasionally are found to be suffering from muscular dystrophy, there are certainly other causes of amyotonia congenita, or the "flabby infant." Every pediatric clinic has followed such infants to complete recovery, even though it may take 2 to 6 years before the child has achieved absolute normality. Autopsies on such recoverable types of amyotonia are rare, and we have little certainty as to the cause of the syndrome in such cases. Occasionally, muscle tenderness in the early stages and, later, contractures of the muscles make it clear that myositis can be a third cause of the amyotonia or "flabby infant" syndrome. Myositis may also be a proximal muscular symmetrical disease in the older infant.

In other infants in whom recovery subsequently occurs, a rise in spinal fluid protein, electromyographic evidence of fibrillation and degeneration of motor units in the muscles give one reason to believe that the initial illness was some type of polyneuropathy.

In the child we are discussing we note that there is some evidence of progression, inspiratory deformity of the sternum, weakened inspiratory sucking and cry, weakness of the extremities giving way to tremors and, ultimately, to paralysis. Progression was very slow for there was substantial weakness present at birth. Intrauterine myositis and polyneuritis are unlikely, and Werdnig-Hoffmann's disease is not severe at birth. We are left, then, with muscular dystrophy as the likely cause. But what kind of muscular dystrophy? Indeed, one may ask if there is anything to be gained by distinguishing the various types of muscular dystrophy. In the adolescent and adult, there is, because the prognosis and the feasibility of planning better use of muscles and rehabilitation depends on knowledge of the natural history of different types of the disease. We can be much more sure, for example, that a Landouzy-Déjerine type of muscular dsytrophy will reach an arrested stage and so give a much better chance for rehabilitation than one of the more progressive types, such as the pseudohypertrophic.

The present case falls into that more amorphous group that is called simply congenital muscular dystrophy. Some of them are rapidly progressive, some of them relatively benign. I know of no way of distinguishing the progressive type from the benign type in the first 6 months of life. After the first 6 months some useful impression as to the rate of progression of the disease may be gained. In general, the more severe the disease the more strongly hereditary it is. In the infant we are discussing, the disease was evidently precocious and severe. I would suspect that there was high liability to the disease in other children born to the same parents, even though there is no known family history.

I conclude therefore that a severe form of congenital progressive muscular dystrophy was the cause of the muscular weakness of this child.

DR. CRAIG.—Dr. Denny-Brown, what about other generations in this type of severe congenital recessive disease?

DR. DENNY-BROWN.—Most usually there is no history of the disease in previous generations. This could indicate a recessive trait that has conjunction of latent liabilities in the two parents, and therefore all the children express the defect. It could also be a mutation of a dominant, or sex-linked, defect with less severe incidence.

DR. CRAIG.—You mentioned the shape of the head. It has seemed to me that many of the Werdnig-Hoffmann cases have a peculiar thin cranium with the anteroposterior diameter greatly increased.

DR. DENNY-BROWN.—A young baby who has never been able to hold his head up develops some flattening of the occiput, so that the head actually becomes shorter. I would not be able to explain why Werdnig-Hoffmann babies should have a long dolichocephalic head, unless they lie habitually on one side.

DR. CRAIG.—Would a biopsy, definitively, give you a differential diagnosis between museular dystrophy and amyotomia of the Werdnig-Hoffmann type?

DR. DENNY-BROWN.—Yes, a biopsy should show the difference. It is not as easy as one might think, in the muscles of a very young child. In neural atrophy of any kind there ought to be isolated groups of muscle fibers in much the same stage of degeneration, distinct from other groups or areas of muscle fiber that are unaffected, because each nerve cell controls a little bundle of muscle fibers. The muscle becomes atrophied, bundle by bundle. In muscular dystrophy, or any primary muscle disease, there is a change in muscle fibers, fiber by fiber, with a haphazard pattern of atrophy scattered through any area of cross section.

DR. CRAIG.—Do you ever get extremely severe cases of muscular dystrophy with loss of whole motor units with secondary neuronal changes in the spinal cord?

DR. DENNY-BROWN.—A few dark-staining anterior horn cells, Dr. Craig. They are not very impressive. The point is that there are plenty of intact motor nerve cells still present.

DR. RANDOLPH BYERS.—I think the question of what to tell a mother about other children is of great importance. Every once in awhile, one of these patients turns out to have clear-cut inflammatory disease of the muscle which you think of as being certainly not genetic in etiology. Knowing this is a great comfort in talking to the mother. When the biopsy specimen shows dystrophy, you are in sort of a box. In a few instances, where a clear-cut dystrophy has turned up on the biopsy, a few mothers have been obstinate and insisted on having other children; they have all had, as Dr. Denny-Brown suggested, a defective child the next time. A few persistent mothers whose children have had the neuronal type of atrophy have wanted to try again; many of them succeeded in having normal children, along with perhaps one or more abnormal children. In Cornelia de Lange's paper,[2] the instances of other affected children were very high in the congenital muscular dystrophy group.

I thought that this case was one of the Werdnig-Hoffmann variety, purely on the basis of statistics.

DR. CRAIG.—How can you judge the diagnosis from the clinical history?

DR. BYERS.—If you are trained in the school of Dr. Cabot, making diagnoses on a statistical basis, you can do pretty well with Werdnig-Hoffmann's disease. I think that, in a general way, the child who is absolutely "collapsed" at birth is probably more likely to have dystrophy rather than Werdnig-Hoffmann disease. I think it is important to observe the baby at the time of birth.

DR. CRAIG.—Dr. Cohen, would you like to say anything about the electromyographic diagnosis in the very young infant?

DR. JONATHAN COHEN.—I do not believe that the various forms of muscular dystrophy can be differentiated by the changes in the myographic tracings. My own feeling is that the electromyograph is an investigative tool, but it has not been helpful as a diagnostic one. Biopsy in this case was not clear cut, but I believe this emphasizes only the proper selection of the area to be biopsied among the weakened muscles.

DR. JOHN CRIGLER.—Would there be any reason to deny a patient like this a trial of Prostigmin to rule out myasthenia gravis?

DR. DENNY-BROWN.—I did not discuss myasthenia gravis because I have never seen it at this age. If the mother suffers from myasthenia gravis, the newborn child may show the condition for a period of two to three weeks, then recover.

DR. ELIZABETH Q. BANKER.—In de Lange's original description, there were nine children and three of these were affected, so that the genetic factor was thought to be an autosomal recessive. But in the cases that we studied, of two male siblings who were the only two children in the family, both were affected with a myopathy which we called dystrophy. The process was not rapidly progressive and appeared to be a very different type, both pathologically, by reason of the abundance of fibrous connective tissue, and clinically, as it lacked the rapidity that one would see in de Lange's type of congenital muscular dystrophy. In the family history of Turner's[3] cases of a relatively nonprogressive dystrophy, of the thirteen siblings, six were affected. Turner compared his cases with those reported by Silvestri,[4] who described two siblings who had hypotonic muscles from birth and an aunt who had a facioscapulohumeral type of dystrophy. However, Turner's and Silvestri's cases and ours[5] are different from the very rapidly progressive type, but I should think, from the cases reported in the literature of this rapidly progressive congenital dystrophy, that the genetic factor would be an autosomal recessive and there would be a good chance, in this case, of having three normal children for one affected.

DR. CRAIG.—The biopsy specimen, as Dr. Cohen said, was not easily labeled, although we finally settled on a diagnosis of dystrophy, using the criteria that Dr. Denny-Brown mentioned, that there were fibers of various sizes within a single muscle bundle.

The muscles at autopsy were grossly thin and flabby and had a more than normal orange tint. All of the muscles sampled from a variety of areas showed a pattern which is very much like that of the biopsy, only more striking (Fig. 1). There was marked

variation in the size of the fiber, loss of fibers, and some increase in the mononuclears and fibrous tissue cells. Both lungs were collapsed at autopsy and there was a minor degree of bronchitis.

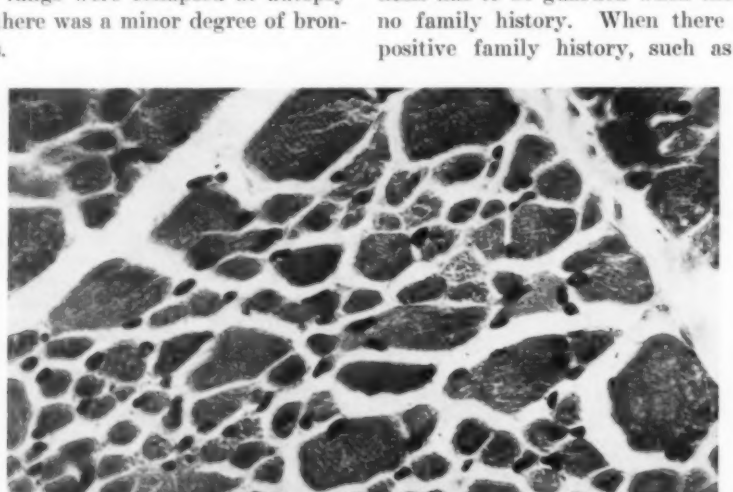

Fig. 1.—Photomicrograph of pectoralis major muscle. Marked variation of fiber size within a single muscle bundle is a prominent feature. (Hematoxylin and eosin; ×500.)

In essence, then, we agree with Dr. Denny-Brown that this case is a muscular dystrophy of the congenital type. I believe that we have had two other cases in different families, Dr. Denny-Brown, in our experience, so this condition is not awfully rare. One of them had an interesting family history. An uncle died in this hospital with muscular dsytrophy and the mother's uncle also died here from the same cause. Here we have a very good typical progressive muscular dystrophy story.

DR. DENNY-BROWN.—There are so few families with the congenital dystrophic type of amyotonia reported in the literature that one cannot find any firm ground for prognosis as to the effect on future pregnancies. Prognosis has to be guarded when there is no family history. When there is a positive family history, such as the cases Dr. Craig mentioned, one can rely to some extent on the principle that the pattern is very much the same in repeated generations.

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Comments on Current Literature

NEUROLOGIC COMPLICATIONS OF ASIAN INFLUENZA

Three pandemics of influenza have occurred within the past seventy years and, in association with each of these pandemics, complications in some patients were reported: pneumonia with and without evidence of secondary bacterial invasion, myocarditis, and central nervous system involvement, occurring in both fatal and nonfatal cases. Neurologic manifestations accompanying or following infection with strains of influenza virus have been classified variously as acute encephalitis, acute disseminated encephalomyelitis, hyperergic encephalomyelitis, and as peripheral neuritis. As a rule, the illness accompanying or preceding these manifestations was described as "grippe," atypical pneumonia, basal pneumonia, etc.; identification of the strain of influenza was based largely on antibody studies.

In recent outbreaks of Asian influenza (strain identified originally as type A/Japan/305/57, and called simply A/Asia/57), the average illness has been neither severe nor prolonged. In some areas, however, the death rate has been high, as for example in the Philippines where the death rate was accounted for in part by the occurrence of complicating bacterial pneumonia and in part by lack of resistance among the general population to this aberrant strain of influenza virus. In some instances of fulminating infection where no secondary bacterial invasion was apparent, autopsy findings have indicated a type of lung involvement which resembles closely that observed experimentally when various strains of influenza virus are administered to mice and ferrets by nasal instillation. Influenza A-57 can be isolated with relative ease by amniotic inoculation in embryonated eggs or by tissue-culture preparations with HeLa or with monkey kidney cells. Where secondary bacterial invasion is a complication of Asian influenza infection, the predominating organism has been *Staphylococcus aureus* with *Hemophilus influenzae* occurring infrequently.

Instances of central nervous system involvement associated with outbreaks of Asian influenza have been appearing in the medical literature periodically since the first recognizable epidemic was reported in the British colony in Hong Kong in April, 1957. One of the earlier reports[1] was in August, 1957, when seven cases of encephalitis among children were described which had occurred at the peak of an epidemic in Bombay. Since January, 1958, neurologic complications in relatively small numbers of patients have been reported with regularity. In one issue of *Lancet* (July 5, 1958) four contributions[2] appear which deal with this subject.

During the epidemic in Bombay[1] which affected both adults and children, 35 children required hospitalization. Thirty of these cases occurred in children between the ages of 6 months and 3 years; no infants under the age of 6 months developed the disease. The clinical course was considerably milder in 28 children over 3 years of age whose cases were treated and followed at home. In the severe cases, hyperpyrexia resistant to hydrotherapy

and antipyretics was a common feature. Of the group of seven patients who developed encephalitis, all had convulsive seizures in addition to high fever; in four the hyperpyrexia was marked; six had extreme restlessness which was not ameliorated by sedatives in high dosage. Polyuria, loss of consciousness, and bulging fontanel were characteristic features in young children. Four of the seven children died. Except for increased pressure, spinal fluid findings were not revealing. Involvement of the hypothalamus was suggested as a possible explanation for the polyuria and hyperpyrexia. In January, 1958, Dubowitz[3] described a severe form of encephalitis in two children which followed a relatively mild influenza-like illness during an epidemic in Surrey, England. Both children were gravely ill and comatose: for three days in one case, and for about 40 hours in the other. There was no significant abnormality in the cerebrospinal fluid. In one of these children only the left side of the body was involved; the other child showed no evidence of lateralizing signs. Both patients made an uneventful recovery once improvement began. Diagnosis of Asian influenza in all these cases was presumptive: by clinical manifestations, by the presence of influenza in epidemic form in the community, and in some instances by increasing titer of type specific antibody (A-57) during the course of clinical recovery.

In the July 5, 1958 issue of *Lancet*, the neurologic complications of Asian influenza were discussed in four separate reports,[2] covering encephalitis; neurologic involvement described as aseptic meningitis; a type of psychotic outburst during the course of the clinical illness in which the patient became extremely restless, noisy, and violent; and a condition following the acute phase which simulated polyneuritis. Encephalitis was perhaps the best documented; fatal cases with a history of convulsions during the clinical illness showed at necropsy marked congestion and edema of the brain. While in most instances microscopic changes in the brain were considered nonspecific, in one recorded case evidence of hemorrhagic encephalitis was noted which was confined to the white matter of the brain. In some cases the presumptive diagnosis was confirmed by isolation of the Asian-type virus from lung tissue, and in one instance from the brain as well. As a rule, signs of encephalitis became apparent about the fourth to the tenth day after onset when the patient seemed to be recovering from the initial illness. Impairment of consciousness was characteristic with bilateral extensor plantor responses, and few or no localizing signs. Spinal fluid findings were within normal limits. Encephalographic tracings showed varying degrees of irregularity with pronounced delta activity, continuous or in bursts. Recovery was usually complete without permanent residuals. In recent American literature also, cases of central nervous system disease associated with Asian influenza have been reported: in March, 1958, three cases[4]; in May, five cases[5]; June and July, four cases[6]; and September, two cases.[7] In most of these cases, the clinical diagnosis was substantiated by complement-fixation and hemagglutination inhibition tests. "In one fatal case, a virus having the properties of a prototype virus of Asian influenza was cultured from the lungs, but not from the central nervous system."[5] Viewing the evidence as a whole, the authors consider it reasonable to assume that the neurologic manifestations in these patients resulted from infection with influenza virus. All are well aware of the various possibilities in this type of central nervous system involvement: that the virus itself is responsible for the encephalitis, that some latent agent may have been activated by the presence of the influenza virus, or that an allergic type of reaction has been evoked by the presence of the virus in the body.

The occurrence of a pandemic of influenza caused by a distinct type-specific strain of virus is of world-wide importance. Central nervous system involvement, added to the more usual complications, makes this disease one to be regarded with caution.

RUSSELL J. BLATTNER.

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News and Notes

Dr. Janet S. Baldwin of New York, head of the Children's Cardiac Clinic at Bellevue Hospital, and Associate Professor of Pediatrics at the New York University College of Medicine, died September 17, 1958, aged 50 years.

The **American Academy of Pediatrics** will grant eighteen or more fellowships to pediatric residents for the fiscal year 1959-1960 and covering a period of six months to one year. These fellowships have been created to enable young physicians, who are legal residents of the United States or Canada and who are in financial need, to complete their pediatric training. The fellowships carry a stipend of $500 to $1,000 depending on the length of time required to complete training and the need. The fellowships have been made possible by a grant to the Academy from Mead Johnson & Company and will be granted as of July 1, 1959. *The deadline for receipt of applications will be March 1, 1959.*

Requirements for the awards: (1) a letter from the Chief of Service indicating that the proposed individual has completed, or will have completed by July 1, 1959, one year of pediatric training credited by the American Board of Pediatrics; that the resident has performed his work ably; and that there is real need for financial assistance; (2) a letter from the resident who is requesting the fellowship stating that he intends to enter pediatric private practice at the conclusion of his residency training.

The fellowship awards are primarily meant to assist those men who intend to enter private, pediatric practice at the conclusion of the two years of approved residency training required for certification by the American Board of Pediatrics. It is recognized, however, that some men may desire a third or fourth year of residency before entering private, pediatric practice. Up to 25 per cent of the fellowships may be awarded to men in this latter category. Consideration will be given to geographic spread of appointments, so that all sections of the country will be represented, and preference will be exhibited for well-qualified but smaller training centers which perhaps have fewer resources for residents in training than do some of the larger centers. Note that research interests and accomplishments, and desire to enter academic pediatrics, are not criteria for the awards.

Members of the Committee on Residency Fellowships of the American Academy of Pediatrics will make final decision on the granting of the awards. Those interested in applying may correspond with the American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill.

Ten *fellowships for medical students for research in clinical nutrition,* sponsored by the **Nutrition Foundation, Inc.,** in cooperation with the Council on Foods and Nutrition of the American Medical Association, are available for 1959. The purpose is to stimulate staff members and students of Schools of Medicine to take a more active interest in the science of nutrition. Each amounts to $200.00 per month for three months.

Conditions: (1) Grant shall be made to a medical student upon recommendation of a senior investigator. (2) Recipient will be selected by the Council. (3) Grant shall be used solely for remuneration of selected medical student. (4) Grant shall be limited to a period not to exceed three months during the non-academic portion of school year. (5) No senior investigator may have more than one student per year receiving a grant. (6) Only a brief progress report or summary will be required. Publication will be at the discretion of the senior investigator.

Application: (1) Application to be made in writing by the senior investigator to: Council on Foods and Nutrition, American

Medical Association, 535 North Dearborn St., Chicago 10, Ill., on or before Dec. 15, 1958. (2) Application shall include: (a) brief outline of study proposed; (b) assurance that adequate physical facilities are available; (c) assurance (but not necessarily identification) of the availability of a qualified medical student.

New York University Post-Graduate Medical School announces a full-time three-week course, Dec. 1-19, 1958, consisting of morning sessions devoted to laboratory instruction in the preparation and standardization of protein extracts, while afternoon sessions in the large outpatient clinic deal with the diagnosis and treatment of asthma, hay fever, and other allergic diseases, the technique of skin tests and hyposensitization, and the role of focal infections in allergy. The course covers not only problems in respiratory but also skin allergy.

Given under the direction of Dr. Abner M. Fuchs. Maximum class 12. For additional information: Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Ave., New York 16, N. Y.

The **Sister Elizabeth Kenny Foundation** announces continuation of its program of post-doctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of the neuromuscular diseases.

The Kenny Foundation Scholars will be appointed annually. Each grant will provide a stipend for a five-year period at the rate of $5,000 to $7,000 a year depending upon the scholar's qualifications. Candidates from medical schools in the United States and Canada are eligible.

Inquiries regarding details of the program should be addressed to: Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, Inc., 2400 Foshay Tower, Minneapolis 2, Minn.

Columbia University, College of Physician and Surgeons, is offering *postgraduate cerebral palsy courses* in the spring of 1959. These courses are designed to (1) acquaint potential leaders in this field with basic knowledge concerning cerebral palsy; (2) review the present status of practical therapy, including the medical, social, educational, and psychological aspects; and (3) point out the controversial features of our present understanding.

Physicians' course: 3 weeks full time. March 2-20, 1959. Fee $100. Includes lectures and demonstrations plus 5 days in cerebral palsy facilities with opportunity for discussion with the physician in charge.

Therapists' and nurses' course: 9 weeks full time. March 2-May 1, 1959. 8 points credit. Fee $210. For occupational, physical, speech therapists and nurses with proper qualifications and experience.

Detailed information may be obtained by writing the College, 630 West 168th St., New York 32, N. Y.

The Department of Pediatrics, University of Washington, School of Medicine, Seattle, announces the establishment of a *research training program* with the collaboration of members of the staffs of the Departments of Biochemistry, Pathology, Anatomy, and Medicine. The program is limited to graduates with the M.D. degree, who are interested in a full-time academic career of research and teaching. Traineeships, supported by the National Institutes of Health, are for a minimum of two years, subject to annual review, and carry stipends up to $6,000 a year dependent upon individual needs. The program for each trainee shall be individually planned by a committee of scientists and shall consist of didactic courses in the physical and biological sciences as well as supervised research training in the laboratories of the Department of Pediatrics. Research work shall be generally in the fields of mammalian embryology, cellular differentiation and metabolism, and growth and development.

Applications for Traineeships to begin during the present year, 1958-1959, will be accepted beginning Sept. 1, 1958. Individuals interested in the program may obtain additional information by writing to the program director: Bruce Mackler, M.D., Department of Pediatrics, University of Washington, School of Medicine, Seattle, Wash.

Books

Pediatric Surgery. Orvar Swenson, New York, 1958, Appleton-Century-Crofts, Inc., 750 pages. Price $20.00.

The new book, *Pediatric Surgery*, by Orvar Swenson should prove a valuable addition to the library of any physician who is interested in the care of children. It should be useful to the pediatrician who needs a reference in regard to surgical conditions seen among his patients; and it should be of great value to those who undertake the actual operative care of infants and children, be it infrequently or as their main surgical interest.

Dr. Swenson is well qualified to write a book on this subject. He is in charge of the surgical service at the Boston Floating Hospital. He was originally trained in the surgery of this age group by Dr. William E. Ladd who provides the foreword to the book. During the past 10 years Dr. Swenson has shared major responsibility for certain advances in technique and in the understanding of a variety of conditions. The best known of these is Hirschsprung's disease, yet he also had made advances in surgery of the esophagus and in the field of genitourinary surgery.

General considerations of the management of the infant and child occupy the first section of the book. The detailed discussion of the methods for handling small patients and their parents during the examination and during the preparation for surgery is very much worth while. The subject of administration of fluids is well covered. The details of how to keep a hypodermic needle in an infant's or child's vein and then how to calculate the fluids to be administered are described clearly and with simplicity. There is an excellent chapter on the techniques which must be used for satisfactory anesthesia.

Following the general discussion of the infant and child in relation to surgical procedures, the author goes on to take up individual surgical problems with details of their surgical management. The subject matter of the volume is arranged anatomically. The conditions met in the head and neck are discussed first, followed by those of the esophagus, then the chest and its various contents; next, the abdomen and the intestinal tract, followed by a section on urology, with lastly relatively short discussions of fractures and miscellaneous lesions of the skin and extremities. Each condition which is covered is described clearly from the clinical point of view, with an explanation which is brief and to the point of how the disease process affects the child.

One of the many excellent features of the book lies in the publisher's handling of the illustrations. The photographs, be they of x-rays, of patients, or of technical procedures, are remarkably clearly printed. The same may be said of the many well-executed drawings which supplement the photographs.

For each surgical condition discussed the author presents one means of surgical treatment which he has found successful. The details of the surgical technique are, as a rule, brought out so that one with a good surgical background and with experience in fine technique should be able to follow the details of procedure.

As in any book covering a wide variety of subjects, certain sections must necessarily be better than others. Of the sections which stand out, three in particular should be mentioned. These include the sections on the esophagus, on Hirschsprung's disease, and on genitourinary surgery. Dr. Swenson's early and successful experience with the treatment of infants with atresia of the esophagus, together with the fact that his mortality figures certainly rank with the best in the world, make the discussion of this problem especially worth while.

The two chapters covering Hirschsprung's disease can be called a classic on the subject. The author's wide experience in handling this

serious condition is presented with great clarity. Not the least valuable part of this discussion is the description of the handling of some of the more serious complications of this abnormality which are not well covered elsewhere. This includes particularly the subject of enterocolitis which so frequently afflicts these children.

The section on urology fills a place which is much needed. Here, again, the author has a large and successful experience with the practical management of these problems. Diagnostic measures are described fully, and surgical procedures are outlined for this group of lesions which are often indifferently handled by those who see these problems only occasionally.

This volume is a clear and thorough presentation of the surgical problems seen in infancy and childhood.

A. H. B.

Laboratory Medicine—Hematology. Dr. John D. Miale, M.D., St. Louis, 1958, The C. V. Mosby Co., 735 pages. Price $13.75.

The high quality of this book from its text to its printing provides one of the most readable, up-to-date collections of hematological data yet published. Without question it should serve an extremely useful purpose in providing students, technologists, pathologists and clinicians alike with the most current "norms," techniques and methods which are nicely integrated with basic physiopathology. The practical manner in which the material has been presented certainly speaks for the familiarity of the author with all the details.

The major portion of the text is a clearly organized progression from basic physiology through morphology and on into disease applications. All of this is well written and thoroughly illustrated with numerous descriptive graphs and charts. Each chapter is duly followed by a valuable detailed listing of the major references.

In most hematological texts, photographs of blood smears and the marrows suffer a loss of detail when presented in black and white, but here the numerous points of value are well documented (i. e., as in the use of bone marrow clot sections to support the smear data). By use of abbreviated case histories accompanying these groups of photographs, a great amount of interest is instilled into what would otherwise be just a collection of beautiful pictures. Color plates are used in illustrating individual cell types and are quite adequate, although there is the usual slight loss of detail technically associated with color reproductions.

Included in the sections on morphology are descriptions of phase microscopy techniques, a mention of electron microscopy, a discussion of supra-vital staining and histochemistry as applied to diagnosis.

Subsequent chapters on erythrocytes, leukocytes and blood coagulation place the stress on hematological pathophysiology throughout, omitting much clinical bulk which would have hindered the basic purpose of this book. The actual detailed methods and techniques are listed in the appendix and are quite current for a field of medicine that is now so rapidly advancing. Following each of these is a useful connecting reference directing the reader back to the location of the text discussion.

In his preface the author states, "It is the function of this book not only to catalogue but also to integrate these facts, and, of greater importance, to induce a system of thinking." He does this in a most admirable manner and this book can strongly be recommended for any laboratory, or in fact for anyone interested in blood.

D. F.

Epilepsy Handbook. Frederic A. Gibbs, M.D., and Frederick W. Stamps, M.D., Springfield, Ill., 1958, Charles C Thomas, Publisher, 101 pages. Price $4.75.

In a very direct and straightforward way the authors have presented a concise handbook on epilepsy, based on a large personal experience. It is intended for the practitioner rather than for the specialist. Brief chapter discussions of the types of epilepsy are followed by an extensive discussion of the many drugs used to control seizures. There is a final chapter on counseling as to living, schools, marriage, etc. The authors state that 80 per cent of the seizures can now be controlled by drugs. While some experts will undoubtedly take issue with some of the authors' statements and conclusions because of their positiveness, the practicing physician will find it a most useful and satisfactory discussion of the disease.

Human Blood in New York City. Committee on Public Health of the New York Academy of Medicine, 2 East 103rd Street, New York 29, N. Y., 147 pages.

A report of an important study of the procurement, distribution, and utilization of blood in New York City, by a committee of the Academy of Medicine. Dr. H. D. Kruse was the General Director of the study. The use of blood for transfusion goes back to the twenties, but it was not until the beginning of World War II in 1941 that it came into extensive use and rapidly grew into a community problem. In New York, as in nearly every other city, it is today a confused problem with many angles, involving the hospitals which have the ultimate responsibility for the use of blood, and the community and commercial blood donor services. The report brings out and stresses the many differences in techniques that exist in the procurement, care, and distribution of blood.

This well-planned and carried out study of the situation existing in New York was participated in by 158 organizations involved in blood-handling. These consisted of 148 hospitals, 9 professional blood banks, and the American Red Cross. In 1956 nearly 350 thousand units of blood were obtained in New York, of which nearly 250 thousand were transfused to patients in the New York hospitals. In all, over 1,000 "full-time-equivalent" persons were employed in the blood-handling work. The report contains many tables of the statistics developed by the study, and excellent graphs. The wide variations in the techniques, records, method of donor recruitment, etc., are brought out. The Committee makes 60 specific recommendations based on the findings of the study. The first of these is that all the blood-handling agencies formally organize, on a permanent basis, a community body concerned with blood.

Blood-handling has grown up in a rather haphazard way in practically every city in the United States. While the problems undoubtedly vary in importance according to the particular city, this thorough study of the situation in New York should serve as a vade mecum to bring order into the rather confused and chaotic conditions existing in many. It is an excellent report that should have a wide study and reading.

Chirurgie infantile d'urgence. Marcel Fèvre, Paris, 1958, Masson & Cie, 718 pages.

A completely rewritten text by the clinical professor of pediatric surgery of the Paris Medical Faculty and surgeon to l'Hôpital des Enfants-Malades. A first edition was published in 1939 and the picture of urgent surgical conditions has quite changed during the intervening years, due to the introduction of the newer drugs and the practical disappearance of some conditions such as typhoid fever. It is a well-written text that discusses many surgical conditions urgently requiring surgical treatment, and will be of interest to the rapidly growing group of pediatric surgeons throughout the world.

The Nursing Mother. Frank Howard Richardson, New York, Tupper and Love, 55 Fifth Avenue. Price $2.95.

As Dr. Richardson emphasizes, infants should be breast-fed up to the age of 6 months if possible, because human milk is the best milk for young infants. It has preventive and therapeutic value, is economical, easily digestible, fresh, free from contamination, automatically produced, and time-saving. It is the safest food for prematures who are mature enough to suckle at the breast. Instances of breast milk "not agreeing with an infant" are almost unknown. Breast feeding provides gratification and a sense of security to babies. Breast feeding also is important physiologically and psychologically to mothers.

The only contraindications to breast feeding are heart, kidney, lung, and psychiatric diseases in the mother. Also, she should not take drugs which pass into her milk, e.g., antibiotics, atropine, barbiturates, bromides, iodides, morphine, salicylates, and sulfonamides.

Most mothers can nurse their infants if they have the desire, proper pre-and postnatal care, adequate sleep, moderate exercise, freedom from worry, and a good pre-and postnatal diet. They should drink 1 quart of milk and an additional quart of

fluid daily, eat fruit, salads, green vegetables, eggs, meat, cod-liver oil or its equivalent, and whole-wheat bread, in 3 to 4 well-balanced meals, and rest at least 1 hour daily in addition to 8 hours at night.

Normal infants suckle and swallow at birth; inability to nurse well is more likely to be due to an imperfect central nervous system than to muscular weakness, except in prematures.

This book is highly recommended to general practitioners, obstetricians, and pediatricians. W. C. D.

Congenital Anomalies of the Hand and Their Surgical Treatment. Arthur J. Barsky, M.D., Springfield, Ill., 1958, Charles C Thomas, Publisher, 165 pages. Price $5.75.

This monograph by the Professor of Clinical Surgery at the Albert Einstein College of Medicine will interest the practitioner as well as the plastic surgeon, and is largely based on the author's personal experience. After a brief résumé of such matters as incidence, etiology, and heredity, the various types of deformities are presented. The text is unusually well illustrated, and it should serve as a valuable book of reference to the physician with a patient who has a congenital anomaly of the hand.

Modern Prescription Drugs: Their Impact on the Family Budget. New York City, 1958, Citizens' Committee for Children of New York City, Inc., 58 pages.

Report of a Committee Study to try and find the answer to certain questions relating to the economic side of drugs. The finding that the cost of drugs is an economic hardship on low-income families is a well-known fact and not new. The use of unnecessary expensive drugs is stressed, and the pressure put on physicians by patients in this connection is acknowledged. Some of the findings and recommendations are not very realistic when considered as a part of the total picture. Thus *smaller quantities* are stressed in prescribing. On page 19 we note that for a prescription using ingredients costing 40 cents, and taking 20 minutes to prepare, the fair and equitable price is $3.00 to the pharmacy. Thus the ingredients and smaller quantity would be of little importance. There are many problems involved in the cost of drugs. Unfortunately the report chiefly calls attention to this rather than offering solutions of value.

Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment, ed. 4. H. J. Parish, M.D., Edinburgh, 1958, E. & S. Livingstone Ltd. (Williams & Wilkins, Baltimore), 256 pages. Price $7.00.

A fourth edition by the Director of the Wellcome Foundation. The text has been extensively revised and enlarged. For example, instead of two chapters on active immunization against virus diseases, the new edition contains five, including one on poliomyelitis. It is an important, rapidly changing and developing field to which this well-known text is an excellent guide.

Les sinusites de l'enfance. J. Terracol and Y. Guerrier, Paris, 1958, Masson & Cie, 166 pages. Price 1,400 fr. (French).

A monograph on sinusitis in childhood, which the authors consider a fairly frequent condition. After a detailed presentation of the anatomy of the sinuses as they develop in childhood, the remainder of the text discusses the clinical aspects. Etiologically, sinusitis is due to infections or to allergy. The authors stress the sharp differences in importance as regards treatment between the acute and chronic forms of the condition. The monograph lacks a good index and bibliography.

The Atomic Age and Our Biological Future. H. V. Brondsted, New York, Philosophical Library, 80 pages. Price $2.75.

This book was reviewed by several because of its unusual nature. It was agreed, in general, that the author (1) has something to say of a most important nature and (2) he says it in a very clear manner. In fact, this little book should make very informative reading to the lay public concerning the implications of the atomic age and the very real nature of the dangers which could confront us. As nearly as could be determined, the book's biological facts and the atomic physics content are quite sound.

Practical Cardiology. Albert S. Hyman, M.D., New York, 1958, McGraw-Hill Book Company, Inc., 307 pages. Price $7.00

Dr. Hyman's *Practical Cardiology* is written for the practitioner rather than a large technical book for the specialist. He discusses the examination of the patient and the application of the newer techniques for the practitioner. It is concerned with the cardiac lesions of the adult rather than those of childhood.

The Nursing of Mental Defectives. Charles H. Hallas, S.R.N., R.M.N., Bristol, 1958, John Wright & Sons, Ltd. (Williams & Wilkins Co. in U. S. A.), 182 pages. Price $5.00.

This is a unique book by the Senior Tutor in charge of the Hortham Hospital for Mental Defectives, near Bristol. It is a valuable guide for those working in institutions for mental defectives.

Essentials of Pediatrics, ed. 6. Philip C. Jeans, M.D., F. Howell Wright, M.D., and Florence G. Blake, R.N. Philadelphia, 1958, J. B. Lippincott Co., 714 pages. Price $6.00.

This widely used text for nurses by the late P. C. Jeans of Iowa first appeared in 1934. Following Dr. Jeans's death, Dr. Wright and Miss Blake, of the University of Chicago, took over the text. This sixth edition has been quite reorganized and modernized.

A Primer of Cerebral Palsy. Joseph D. Russ, M.D., and Hyman R. Soboloff, M.D., Springfield, Ill., 1958, Charles C Thomas, Publisher, 77 pages. Price $4.00.

There has been a steady flow of texts on cerebral palsy in recent months. The term, "A Primer" aptly describes its contents.

Paediatrics for Nurses, ed. 2. Arthur G. Watkins, M.D., Bristol, 1958, John Wright and Sons, Ltd. (Williams & Wilkins Co. in U. S. A.), 200 pages. Price $3.75.

A revised text for nurses by the Professor of Child Health at the Welsh National School of Medicine in Cardiff. First published in 1947.

Handbook of Treatment of Acute Poisoning, ed. 2. E. H. Bensley, M.D., and G. E. Joron, M.D., Edinburgh, 1958, E. & S. Livingstone Ltd. (Williams & Wilkins, Baltimore), 212 pages. Price $4.00.

A second edition of this small book intended as a guide to treatment.

Principles of Internal Medicine, ed. 3. Edited by T. R. Harrison, M.D., New York, 1958, McGraw-Hill Book Company, Inc., 1839 pages. Price $18.50.

A new revised edition of Harrison's text. (Last in 1954.) Over 100 internists have contributed chapters.

Principles of Internal Medicine, ed. 3. Edited by T. R. Harrison, M.D., New York, 1958, McGraw-Hill Book Company, Inc., 1839 pages. Price $18.50.

A new, revised edition (last edition in 1954). Over 100 internists have contributed chapters.

Pediatric Gynecology, ed. 4. Goodrich C. Schauffler, M.D., Chicago, 1958, Year Book Publishers, Inc., 349 pages. Price $9.00.

A revised enlarged edition last published in 1953.

Guide to Summer Camps and Summer Schools. Boston, 1958, Porter Sargent Publisher, 160 pages. Price $2.20.

The 1958-1959 edition of the useful directory of summer camps and schools.

Editor's Column

HAIL AND FAREWELL

WITH this issue the Editor puts aside his pencil and closes his desk. Looking back over the twenty-seven years of Editorship it has been a life with occasional periods of worry, stress, and dissatisfaction, but with never a moment of boredom.

Our thoughts have been turning back to the birth of the JOURNAL in 1932, when we were inveigled into taking on an unwanted task. The Academy of Pediatrics was in its infancy with a few hundred members, impecunious, and regarded with skepticism by many pediatricians. It was in fact being kept alive by the devoted nursing of one man—Cliff Grulee—aided by a relatively small group who had been responsible for its formation. The "American Board," in which the Editor-to-be was deeply involved, was in the midst of labor pains. This was the pediatric setting.

At one of those "bull sessions" back in 1931, discussing the welfare of the medical world and of pediatrics in particular, the Editor-to-be expressed the opinion that what was needed for the Academy to advance the purposes for which it was founded was some method of intercommunication among the membership, as an Academy-sponsored pediatric journal. There was general agreement and it was decided to explore the idea. The exploration was rather disheartening. The country at that time was in a period of deep depression—not a simple "recession" as at present. A number of medical publishers were approached with the idea, and all but one held up their hands with horror at the mere thought of starting a new medical journal under existing economic conditions. The lone exception was C. V. Mosby, Sr., of St. Louis. "Doc" Mosby, as he was known to many of us, was an optimist with an uncanny vision. He believed that pediatrics was a coming field, and that sooner or later a pediatric journal sponsored by the Academy would be a success. He finally proposed to assume all financial responsibility for a new journal, provided the Academy would assume complete medical responsibility—Editor, Editorial Board, material for publication, etc.—and the entire membership subscribe to the journal at a club rate to be collected by the Academy. The Academy decided to accept the offer and added the subscription to the dues of each member. The possibility or thought of any profits ever rising from such a journal never entered our minds. What we were solely interested in was to establish a journal to

advance pediatrics and the purposes for which the Academy was founded. A conversation at that time comes to mind in which my statement was to the effect that a circulation of 3,000 might possibly be reached at some time in the dim future. The opinion of "Doc" that it might reach 5,000 sounded like a delusion of grandeur. He did not live to see it reach 10,000. Incidentally while on the subject, the Mosby Company had to make up a deficit for the first half-dozen years, and then for the next few years broke even on the venture. No one could foresee at that time the amazing development of pediatrics that was in the making nor the tremendous development of commercial products for infant and child care that led to pediatric journals becoming highly desirable advertising media. The two together have made pediatric journals financially profitable. No more could we foresee the tremendous growth of the Academy that would take place, the important position it would come to occupy, and the extent of its interests and activities.

Then the Academy had to get down to "brass tacks" to fulfill its part of the contract. The opinion was that in these early years the Editor should be someone from St. Louis in order to simplify the inevitable conferences between the Academy and publisher that would be necessary in launching the new journal. This was the reason that led to the retiring Editor assuming the task. There was strenuous objection on his part for a number of reasons. Not only was there no interest in editorial work together with a complete lack of preparation, but there were a number of pediatric activities outside of practice and teaching in which he was interested and busy. Pressure was applied—"your idea," "duty to the Academy," and that sort of thing—and so reluctantly an agreement was made to take on the Editorship *for two years* to get the journal started, provided Hugh McCulloch would join with him and take over certain parts of the work and responsibility. McCulloch agreed, and so in January of 1932 the editorial work got underway, with the first issue appearing in July of that year. For one reason or another the "challenge" of the Editorship never seemed to come to an end, and the years stretched on and on.

Much could be written about these twenty-seven years as they were filled with incident, but it is water over the dam. In 1946 the Academy decided to withdraw its sponsorship of the JOURNAL and start its own pediatric journal. It was a decision based entirely on financial considerations. The Editor's decision to decline the request of the Academy to take on the Editorship of the new journal was a difficult one to make. Two reasons chiefly influenced the decision. One was the reluctance to start a new journal with a new publisher and again go through the headaches of those early years when the JOURNAL was being launched. The second was more involved. In the early years when the JOURNAL was young and struggling for existence, the entire management was left to the Editor and Editorial Board. As it became successful and prosperous, and as the Academy and circulation of the JOURNAL increased in size, the Executive Board of the Academy began to

take an interest, with an increasing tendency to feel it was their function to determine the editorial policies of the JOURNAL to be followed by the Editor and Editorial Board. The Editor, being by temperament rather independent in his thinking and actions, as his friends have joshed him many times, was finding it difficult and at times irritating to try and serve two masters—the two Boards—with at times quite divergent ideas as to Editorial policies.

The decision to continue on with the Editorship of the JOURNAL, from which he had resigned at that time along with the rest of the Academy-appointed Editorial Board, was due to a steadily growing feeling that there was and always would be need for independent medical journals which did not have to follow policies dictated by the governing Board of a medical society or organization, and thus are open to a free discussion of all sides of problems and topics of medical importance and interest. Too often the dictated policies reflected a political background or bias. Pages could be written, citing incidents to support this viewpoint. In fact, one of the principal reasons for the formation of the Academy was to provide a forum for the expression of independent viewpoints regarding pediatric matters, following the passing of a rule in 1922 by the governing body of the A. M. A. prohibiting the Sections from discussing or passing resolutions relating to their own special fields of practice and knowledge, and restricting their work to purely scientific discussion. Freedom of expression and the opportunity to present differing viewpoints are essential to sound progress. It was for this reason the Editor decided to continue with the Editorship of the JOURNAL as an independent journal, with an Editorial Board in complete control of the editorial policies. Never once in the twenty-seven years have the Publishers attempted to influence the Editor or Editorial Board in any way. They have cooperated fully with every request and decision as to policy made by the Board. It has been a most happy relationship.

Some three years ago the Editor requested the Editorial Board to select an Editor to succeed him. He would soon reach the age of 75 and was retiring from practice. The time had been reached when the tasks and responsibilities of the Editorship should be taken over by a younger man. He knows of no one more fitted to take over than the selection of the Board. "Bill" Nelson is so well known to the pediatricians that he needs no introduction or *curriculum vitae*. There is, incidentally, great personal satisfaction after these twenty-seven years in knowing the Editorship is in such capable hands. The retiring Editor, in saying "Farewell," can only express his indebtedness to the pediatricians in all parts of the world for the fine and happy relationships he has had with them over the years. It is, however, to his pediatric colleagues and friends who have served on the Editorial Board during his twenty-seven years of Editorship that he is most indebted. Without their constant and ever-ready help and advice it would have been an impossible task.

B. S. V.

TRANQUILIZERS

The Psychopharmacology Service Center of the National Institute of Mental Health provided the Sub-committee of the Committee on Appropriations of the United States Senate with a review of new drugs for the treatment of psychiatric conditions.* The statement was based on the Center's review of the literature and discussions with clinical investigators and representatives of pharmaceutical firms. The Center emphasized that their report should not be considered as providing any final or definitive appraisal of any of the compounds mentioned.

In the spring of 1956, only three tranquilizing drugs were of any considerable prominence—chlorpromazine (Thorazine), reserpine (Serpasil, Reserpoid, etc.), and meprobamate (Miltown, Equanil). During the past year, there has been a striking expansion in the number of such drugs available and the Center's report summarized the present state of this field.

TRANQUILIZERS

Phenothiazine Derivatives
- Chlorpromazine (Thorazine)
- Promazine (Sparine)
- Mepazine (Pacatal)
- Prochlorperazine (Compazine)
- Perphenazine (Trilafon)
- Thiopropazate (Dartal)
- Triflupromazine (Vesperin)
- Promethazine (Phenergan)

Reserpine (Serpasil, Reserpoid, etc.)
- Deserpidine (Harmonyl)
- Reserinnamine (Moderil)

Mild Tranquilizers

Sedative Central Muscle Relaxants
- Meprobamate (Miltown, Equanil)
- Hydroxyzine (Atarax)
- Azacyclonol (Frenquel)
- Benactyzine (Suavitil)
- Phenyltoloxamine (PRN)
- Phenaglycodol (Ultran)

PHENOTHIAZINE DERIVATIVES

All of the phenothiazine derivatives seem to share the tranquilizing effect on disturbed psychotic patients possessed by chlorpromazine. The major undesirable effects that have been observed with chlorpromazine (Thorazine) are: (1) parkinsonian symptoms including muscular rigidity, tremor, and other neurological symptoms that can occur in more than half of all patients treated if very large doses are used; it is observed in 5 to 10 per cent of patients treated more conservatively and ceases if medication is reduced or stopped; (2) transient jaundice which occurs in 1 per cent of patients; (3) agranulocytosis, which is rare and more serious with an incidence of perhaps one of every two to ten thousand patients.

With the newer derivatives, in general, jaundice has not been observed, but with some agranulocytosis has occurred. The parkinsonian and other neurological symptoms have continued with most of these agents as with chlorpromazine.

The Psychopharmacology Service Center concluded: (1) "It is difficult at this time to tell whether any of these compounds possess any dramatic superiority over the others." (2) "Sufficient information is not yet available

*Hearings before the Sub-committee of the Committee on Appropriations, United States Senate, on H.R. 11645. United States Government Printing Office, Washington 808-810, 1958.

to judge reliably the relative safety of all these drugs. The incidence of serious blood dyscrasias and other side effects suggests that these drugs be used clinically with considerable caution and close medical supervision."

RESERPINE-LIKE DRUGS

Early clinical studies would indicate that both of the new reserpine-like drugs are somewhat more potent and with fewer side effects than reserpine. In general, the phenothiazines act more rapidly but "the whole problem of the relative merits of this group of drugs as compared to the phenothiazines in the treatment of disturbed patients is still open."

OTHER TRANQUILIZING DRUGS—SEDATIVE CENTRAL MUSCLE RELAXANTS

These compounds generally are simpler molecules than the phenothiazine derivatives and are in clinical use in the treatment of nonhospitalized neurotic patients. "The place for these drugs in the therapeutic regimen of the mentally ill has yet to be established." "The Center's advisors and its staff have been concerned by the paucity of studies, controlled or otherwise, of drug effectiveness in neurotic or other non-hospitalized patients."

The unbiased testimony of the authorities of the National Institute of Mental Health on the therapeutic value and untoward effects of the increasing number of tranquilizing drugs should guide the physician through the maze of claim and counterclaim.

Unquestionably, these agents will assume an important place in the pediatric armamentarium. Already the advertising pages of our pediatric journals recommend various ones of these drugs to stop vomiting "from virtually any cause"; to promote sound uninterrupted sleep; for behavior disorders and problem children; to relieve anxiety, tension and fear; to treat irritability, excessive anger, and failure to communicate adequately; to provide a mild and selective shield against stress in the overactive, fearful, rebellious child; to help him eat and sleep better; to make him more amenable to parental guidance; to control the emotional component of allergies; to relieve mental and muscular tension; for temper tantrums, ties, stuttering, asthma, hyperkinesia, nightmares, enuresis; and to give peace of mind.

In hopefully weighing all of these claims, it would give the pediatrician peace of mind if the pace were not so fast and if sufficient time had elapsed to allow confirmation by controlled studies and a realistic appraisal of the possible undesirable effects.

It is reassuring to know that the National Institute of Mental Health is exploring methods for setting up a feasible and informative system for the reporting of toxic reactions to psychiatric drugs in a continuing manner. It has assisted in the planning and is supporting three well-controlled studies to compare the clinical attributes of the various phenothiazine derivatives. It is supporting a controlled study to investigate the effectiveness of reserpine and chlorpromazine in acutely ill psychiatric patients. The Center and its advisors are developing adequate methods for assessing change in patients as a necessary first step to the stimulation of clinical studies in this area.

Of more immediate interest to pediatricians, the Psychopharmacology

Service Center is organizing a conference on "Child Research in Psychopharmacology" to be held in Washington on Oct. 27-28, 1958. The conference will consider drug effects on psychological functions, family relationships and community adjustments, maturation processes, and central nervous system behavior. It will consider the effect of these drugs on the "behavior problem"; on the organically impaired, mentally defective, speech problem child, and on the normal child. It will consider research methodology and measuring instruments. The conference will develop new hypotheses and approaches to the study of drug effects in children; it will pave the way for initiating long-term developmental studies of drug effects in children; and it will attempt to stimulate research interest in competent investigators.

The future role of tranquilizers in pediatric practice is of great promise. For the present, "make haste slowly" and exercise sound medical judgment. It is not yet the time to make tranquilizers a standard ingredient of the infant's formula—as was once, believe it or not, done in certain parts of the country with phenobarbital.

S. H. C.

INDEX TO VOLUME 53

AUTHORS INDEX*

A

ABBASSY, A. SHAFIK, MASSOUD, GAMAL-EL-DINE, AND RIDA, AMIN, Hand-Schüller-Christian disease, 233

ADAMS, FORREST H. (WITH FINK, BURTON W., MOSS, ARTHUR J., AND O'LOUGHLIN, BERNARD J.), Right heart catheterization in infants and children, 566

AFTAHI, FARHANG (WITH AMERMAN, E. E., AND BRESCIA, MICHAEL A.), Ferrous sulfate poisoning, 476

AMERMAN, E. E., BRESCIA, MICHAEL A., AND AFTAHI, FARHANG, Ferrous sulfate poisoning, 476

ARMSTRONG, JAMES G., Acute gastroenteritis, 704

ASAY, LYAL D. (WITH KOCH, RICHARD), Oleandomycin, a laboratory and clinical evaluation, 676

ASSEVERO, VICTOR L., AND MOSS, JAMES M., Diabetes mellitus in infancy, 227

AZAN, LUIS (WITH CASTELLANOS, AGUSTIN, CALVIÑO, JOSE M., AND CASTELLANOS, AGUSTIN, JR.), Supraventricular tachycardia simulating ventricular paroxysmal tachycardia in infancy, 285

B

BATES, TALCOTT, AND GRUNWALDT, EDGAR, Myofascial pain in childhood, 198

BATSON, RANDOLPH, AND CHRISTIE, AMOS, Immunization methods and materials, 51

BAUMGARTNER, RUTH J. (WITH BRADLEY, J. EDMUND), Subsequent mental development of children with lead encephalopathy, as related to type of treatment, 311

BEHRER, M. REMSEN (WITH GOLDRING, DAVID, BROWN, GEORGE, AND ELLIOTT, GLADDEN), Rheumatic pneumonitis. Part II. Report on the clinical and laboratory findings in twenty-three patients, 547

BLANCO, RAMON L. (WITH ESPINOSA, RENATO R., AND PICORNELL, BARTOLOME V.), Prolapsing trigonal mucosa in infant, 446

BLATTNER, RUSSELL J., Adenovirus pneumonia, 631

—, Ardmore disease: a new clinical entity? 249

—, Correspondence, 253

—, Environmental penicillin and penicillin-resistant Staphylococcus aureus, 131

—, Mammalian viruses and rickettsiae: new methods of purification and recovery, 503

—, Necrotic arachnidism, 377

—, Neurologic complications of Asian influenza, 751

BOGIN, MAXWELL, GOTTFRIED, SIDNEY P., LEVYCKY, NICHOLAS V., AND GRAF, CURT, Serum bilirubin levels in the newborn infant and their relation to clinical icterus and liver function studies, 529

BONGIOVANNI, ALFRED M., MELLMAN, WILLIAM J., AND EBERLEIN, WALTER R., The proper use of adrenal hormonal drugs in pediatric practice, 3

BOWERS, DORRANCE, Correspondence, 635

BRADLEY, J. EDMUND, AND BAUMGARTNER, RUTH J., Subsequent mental development of children with lead encephalopathy, as related to type of treatment, 311

BRESCIA, MICHAEL A. (WITH AMERMAN, E. E., AND AFTAHI, FARHANG), Ferrous sulfate poisoning, 476

BRITT, ROBERT L. (WITH WARNER, CHARLES L., AND RILEY, HARRIS D., JR.), Bronchopulmonary sequestration in infancy and childhood, 521

BRODER, HAROLD M., Prognosis in Legg-Perthes disease, 451

BROWN, GEORGE (WITH GOLDRING, DAVID, BEHRER, M. REMSEN, AND ELLIOTT, GLADDEN), Rheumatic pneumonitis. Part II. Report on the clinical and laboratory findings in twenty-three patients, 547

BUSH, LOUIS G., Medicine at an American Indian reservation, 622

C

CALVIÑO, JOSE M. (WITH CASTELLANOS, AGUSTIN, AZAN, LUIS, AND CASTELLANOS, AGUSTIN, JR.), Supraventricular tachycardia simulating ventricular paroxysmal tachycardia in infancy, 285

CANN, HOWARD M., AND VERHULST, HENRY L., The salicylate problem with special reference to methyl salicylate, 271

CANTLIN, M. L., ROMINGER, C. JULES, AND O'SULLIVAN, WARD D., Surgical treatment of some pulmonary conditions in childhood, 432

*July, pp. 1-138; August, pp. 139-258; September, pp. 259-388; October, pp. 389-514; November, pp. 515-644; December, pp. 645-776.

CASTELLANOS, AGUSTIN, AZAN, LUIS, CALVIÑO, JOSE M., AND CASTELLANOS, AGUSTIN, JR., Supraventricular tachycardia simulating ventricular paroxysmal tachycardia in infancy, 285

CASTELLANOS, AGUSTIN, JR. (WITH CASTELLANOS, AGUSTIN, AZAN, LUIS, AND CALVIÑO, JOSE M.), Supraventricular tachycardia simulating ventricular paroxysmal tachycardia in infancy, 285

CHOREMIS, C., AND NICOLOPOULOS, D., Serum and urine amino acids in infantile toxicosis, 515

CHRISTIE, AMOS (WITH BATSON, RANDOLPH), Immunization methods and materials, 51

CLARKE, MAIRIN (WITH EHRLICH, R. M., AND TURNER, J. A. P.), Neonatal varicella, 139

COLBERT, EDWARD G., AND KOEGLER, RONALD R., Toe walking in childhood schizophrenia, 219

COPPRIDGE, ALTON J., AND RATLIFF, RIGDON K., Unilateral multicystic kidney disease, 330

CRAWFORD, LLOYD V., Treatment of allergic eczema versus seborrheic infantile eczema, 99

D

DAESCHNER, C. W., JR. (WITH DAESCHNER, G. L., AND MATTHES, F. T.), Treatment of nausea and vomiting in children with prochlorperazine, 148

DAESCHNER, G. L., MATTHES, F. T., AND DAESCHNER, C. W., JR., Treatment of nausea and vomiting in children with prochlorperazine, 148

DAVIS, H. CLINTON (WITH QUILLIAN, WARREN W., AND LANCASTER, JAMES W.), Methemoglobinemia associated with intestinal strangulation obstruction in the newborn infant, 737

DEYOUNG, VERNON R., Hydramnios as a signal to the physician responsible for newborn infants, 277

DIAMOND, LOUIS K. (WITH PEARSON, HOWARD A.), Chronic monocytic leukemia in childhood), 259

E

EBERLEIN, WALTER R. (WITH BONGIOVANNI, ALFRED M., AND MELLMAN, WILLIAM J.), The proper use of adrenal hormonal drugs in pediatric practice, 3

EHRLICH, R. M., TURNER, J. A. P., AND CLARKE, MAIRIN, Neonatal varicella, 139

ELLIOTT, GLADDEN (WITH GOLDRING, DAVID, BEHRER, M. REMSEN, AND BROWN, GEORGE), Rheumatic pneumonitis. Part II. Report on the clinical and laboratory findings in twenty-three patients, 547

ESPINOSA, RENATO R., BLANCO, RAMON L., AND PICORNELL, BARTOLOME V., Prolapsing trigonal mucosa in infant, 446

ETTELDORF, JAMES N., Editorial comments on Therapeutic Issue, 1

—, MISSIRLIU, CONSTANTIN, AND FLEISCHMANN, WALTER, Adrenogenital syndrome due to congenital virilizing adrenal hyperplasia, 389

— (WITH MISSIRLIU, CONSTANTIN, AND MISSIRLIU, MARIE F.), Rocky Mountain spotted fever in children, 303

F

FAIRCHILD, JOHN P., GRABER, CHARLES D., VOGEL, EDWARD H., JR., AND INGERSOLL, ROBERT L., Flora of the umbilical stump, 538

FIELDING, ROBERT T. (WITH PEROU, MAURICE L., AND NELSON, HAROLD M.), Leptomeningitis due to Gaffkya tetragena, 484

FINK, BURTON W., MOSS, ARTHUR J., ADAMS, FORREST H., AND O'LOUGHLIN, BERNARD J., Right heart catheterization in infants and children, 566

FLEISCHMANN, WALTER (WITH ETTELDORF, JAMES N., AND MISSIRLIU, CONSTANTIN), Adrenogenital syndrome due to congenital virilizing adrenal hyperplasia, 389

FROMME, DALORES (WITH WHEELER, JAMES E., PLOTKIN, ROBERT F., AND SMITH, NANCY), Acute upper respiratory disease: clinical and bacteriological response to short-term treatment with penicillin V, 571

G

GEPPERT, LEO J. (WITH SCHERZ, ROBERT G.), Recognition and treatment of adrenal crises in the newborn infant, 645

GERHARD, A. M., AND THELANDER, H. E., Cerebral angiomatosis, 586

GILBERT, ENID F., AND RAINEY, JOHN R., JR., Meconium peritonitis caused by a rupture of a Meckel's diverticulum in a newborn infant, 597

GOLDFARB, DONALD L. (WITH SENZ, EDWARD H.), Coma in a child following use of isopropyl alcohol in sponging, 322

GOLDRING, DAVID, BEHRER, M. REMSEN, BROWN, GEORGE, AND ELLIOTT, GLADDEN, Rheumatic pneumonitis. Part II. Report on the clinical and laboratory findings in twenty-three patients, 547

GOTTFRIED, SIDNEY P. (WITH BOGIN, MAXWELL, LEVYCKY, NICHOLAS V., AND GRAF, CURT), Serum bilirubin levels in the newborn infant and their relation to clinical icterus and liver function studies, 529

GRABER, CHARLES D. (WITH FAIRCHILD, JOHN P., VOGEL, EDWARD H., JR., AND INGERSOLL, ROBERT L.), Flora of the umbilical stump, 538

GRAF, CURT (WITH BOGIN, MAXWELL, GOTTFRIED, SIDNEY P., AND LEVYCKY, NICHOLAS V.), Serum bilirubin levels in the newborn infant and their relation to clinical icterus and liver function studies, 529

GRAVEN, STANLEY N., AND TOMSOVIC, EDWARD J., Celiac disease: response to a gluten-free diet, 726

GRAY, LAMAN A. (WITH KOTCHER, EMIL, AND KELLER, KENNETH), A microbiological study of pediatric vaginitis, 210

GRAY, STEPHEN W. (WITH LIONAKIS, BASIL, SKANDALAKIS, JOHN E., AND HOPKINS, W. A.), Empyema in children, 719

GRUNWALDT, EDGAR (WITH BATES, TALCOTT), Myofascial pain in childhood, 198

H

HAMMOND, KEITH, Correspondence, 381

HOLOWACH, JEAN, AND THURSTON, DON L., A clinical evaluation of acetazolamide (Diamox) in the treatment of epilepsy in children, 160

HOPKINS, W. A. (WITH LIONAKIS, BASIL, GRAY, STEPHEN W., AND SKANDALAKIS, JOHN E.), Empyema in children, 719

HUGHES, JAMES G., AND JABBOUR, J. T., The treatment of the epileptic child, 66

I

ILLINGWORTH, R. S., Obesity, 117

INGERSOLL, ROBERT L. (WITH FAIRCHILD, JOHN P., GRABER, CHARLES D., AND VOGEL, EDWARD H., JR.), Flora of the umbilical stump, 538

J

JABBOUR, J. T., SHEFFIELD, JAMES A., AND MONTALVO, J. M., Severe neurological manifestations in four children receiving Compazine (prochlorperazine), 153

— (WITH HUGHES, JAMES G.), The treatment of the epileptic child, 66

JACOBS, SYDNEY, AND PAPPERMAN, SOL M., Studies on the pH of the respiratory tract. I. Endotracheal aspirate of the healthy newborn infants, 298

JAVID, HUSHANG (WITH TOMSOVIC, EDWARD J.), Cicatricial stenosis of the esophagus following ingestion of a single urine-sugar reagent tablet, 608

JONES, MALCOLM D., SAKAI, HSAJIQ, AND ROGERSON, ALEXANDER G., Intravenous cholangiography in children with fibrocystic disease of the pancreas, 172

JUNG, RODNEY C., The management of intestinal parasitic infections, 89

K

KAMIN, SHELDON H., LLEWELLEYN, CHARLEY JACKSON, AND SLEDGE, WINNIE L., Group dynamics in the treatment of epilepsy, 410

KATZ, BEN E., Education of cerebral palsied children, 467

KELLER, KENNETH (WITH KOTCHER, EMIL, AND GRAY, LAMAN A.), A microbiological study of pediatric vaginitis, 210

KEMPE, C. HENRY, Pediatric use of antibacterial agents, 19

KHALIL, MOSTAFA, The circulating eosinophil level in the newborn infant following normal and difficult labor, 662

KIMSEY, LETITIA S., The bacteriological diagnosis of childhood tuberculosis using bone marrow and peripheral blood aspirates, 413

KIRK, E. WALTON (WITH THELANDER, H. E., AND PHELPS, JANE K.), Learning disabilities associated with lesser brain damage, 405

KLINE, ALLEN H., Incarceration of Meckel's diverticulum in an inguinal hernia, 479

KOCH, RICHARD, AND ASAY, LYAL D., Oleandomycin, a laboratory and clinical evaluation, 676

KOEGLER, RONALD R. (WITH COLBERT, EDWARD G.), Toe walking in childhood schizophrenia, 219

KOTCHER, EMIL, KELLER, KENNETH, AND GRAY, LAMAN A., A microbiological study of pediatric vaginitis, 210

L

LANCASTER, JAMES W. (WITH QUILLIAN, WARREN W., AND DAVIS, H. CLINTON), Methemoglobinemia associated with intestinal strangulation obstruction in the newborn infant, 737

LASLETT, PATRICIA A. (WITH POLLOCK, ADRIAN Q.), Cerebral arteriovenous fistula producing cardiac failure in the newborn infant, 731

LEVYCKY, NICHOLAS V. (WITH BOGIN, MAXWELL, GOTTFRIED, SIDNEY P., AND GRAF, CURT), Serum bilirubin levels in the newborn infant and their relation to clinical icterus and liver function studies, 529

LIONAKIS, BASIL, GRAY, STEPHEN W., SKANDALAKIS, JOHN E., AND HOPKINS, W. A., Empyema in children, 719

LLEWELLEYN, CHARLEY JACKSON (WITH KAMIN, SHELDON H., AND SLEDGE, WINNIE L.), Group dynamics in the treatment of epilepsy, 410

M

MCCONNELL, E. M., A case of malignant sacrococcygeal teratoma, 489

MACKENZIE, ELLEN P., The treatment of anorexia, 187

MARTIN DU PAN, R., The vaccination of the newborn infant against pertussis, 180

MASSOUD, GAMAL-EL-DINE (WITH ABBASSY, A. SHAFIK, AND RIDA, AMIN), Hand-Schüller-Christian disease, 233
MATTHES, F. T. (WITH DAESCHNER, G. L., AND DAESCHNER, C. W., JR.), Treatment of nausea and vomiting in children with prochlorperazine, 148
MEISTER, G. S., Correspondence, 507
MELLMAN, WILLIAM J., Influenza encephalitis, 292
— (WITH BONGIOVANNI, ALFRED M., AND EBERLEIN, WALTER R.), The proper use of adrenal hormonal drugs in pediatric practice, 3
MEYERRIECKS, NORMA (WITH WAGNER, RICHARD, AND SPARACO, ROSE), Glycogen storage disease, 683
MIDDELKAMI, J. NEAL (WITH ROMAN, LIWANAG P.), Narcotic addiction in a newborn infant, 231
MISSIRLIU, CONSTANTIN, MISSIRLIU, MARIE F., AND ETTELDORF, JAMES N., Rocky Mountain spotted fever in children, 303
— (WITH ETTELDORF, JAMES N., AND FLEISCHMANN, WALTER), Adrenogenital syndrome due to congenital virilizing adrenal hyperplasia, 389
MISSIRLIU, MARIE F. (WITH MISSIRLIU, CONSTANTIN, AND ETTELDORF, JAMES N.), Rocky Mountain spotted fever in children, 303
MONTALVO, J. M. (WITH JABBOUR, J. T., AND SHEFFIELD, JAMES A.), Severe neurological manifestations in four children receiving Compazine (prochlorperazine), 153
MOSS, ARTHUR J. (WITH FINK, BURTON W., ADAMS, FORREST H., AND O'LOUGHLIN, BERNARD J.), Right heart catheterization in infants and children, 566
MOSS, JAMES M. (WITH ASSEVERO, VICTOR L.), Diabetes mellitus in infancy, 227
MURPHY, DOUGLAS P. (WITH RUBIN, ALAN), Studies in human reproduction. III. The frequency of congenital malformations in the offspring of nondiabetic and diabetic individuals, 579

N

NELSON, HAROLD M. (WITH PEROU, MAURICE L., AND FIELDING, ROBERT T.), Leptomeningitis due to Gaffkya tetragena, 484
NICOLOPOULOS, D. (WITH CHOREMIS C.), Serum and urine amino acids in infantile toxicosis, 515

O

OECONOMOPOULOS, CHRIS T., Perforated duodenal ulcer in an infant, 324
OETTINGER, LEON, JR., The use of deanol in the treatment of disorders of behavior in children, 671
OLMSTED, RICHARD W., Dermal fistulas of dental origin in children, 229
O'LOUGHLIN, BERNARD J. (WITH FINK, BURTON W., MOSS, ARTHUR J., AND ADAMS, FORREST H.), Right heart catheterization in infants and children, 566
O'SULLIVAN, WARD D. (WITH CANTLIN, M. L., AND ROMINGER, C. JULES), Surgical treatment of some pulmonary conditions in childhood, 432

P

PAPPERMAN, SOL M. (WITH JACOBS, SYDNEY), Studies on the pH of the respiratory tract. I. Endotracheal aspirate of the healthy newborn infants, 298
PEARSON, HOWARD A., AND DIAMOND, LOUIS K., Chronic monocytic leukemia in childhood, 259
PEROU, MAURICE L., FIELDING, ROBERT T., AND NELSON, HAROLD M., Leptomeningitis due to Gaffkya tetragena, 484
PHELPS, JANE K. (WITH THELANDER, H. E., AND KIRK, E. WALTON), Learning disabilities associated with lesser brain damage, 405
PICORNELL, BARTOLOME V. (WITH ESPINOSA, RENATO R., AND BLANCO, RAMON L.), Prolapsing trigonal mucosa in infant, 446
PINKEL, DONALD (WITH STICKLER, GUNNAR B.), Calculation of nutritional allowances for infants and children on the basis of body surface, 464
PLOTKIN, ROBERT F. (WITH WHEELER, JAMES E., FROMME, DALORES, AND SMITH, NANCY), Acute upper respiratory disease: clinical and bacteriological response to short-term treatment with penicillin V, 571
PLOTKIN, STANLEY A., Correspondence, 253
POLLOCK, ADRIAN Q., AND LASLETT, PATRICIA A., Cerebral arteriovenous fistula producing cardiac failure in the newborn infant, 731

Q

QUILLIAN, WARREN W., LANCASTER, JAMES W., AND DAVIS, H. CLINTON, Methemoglobinemia associated with intestinal strangulation obstruction in the newborn infant, 737

R

RAINEY, JOHN R., JR. (WITH GILBERT, ENID F.), Meconium peritonitis caused by a rupture of a Meckel's diverticulum in a newborn infant, 597
RATLIFF, RIGDON K. (WITH COPPRIDGE, ALTON J.), Unilateral multicystic kidney disease, 330
RIDA, AMIN (WITH ABBASSY, A. SHAFIK, AND MASSOUD, GAMAL-EL-DINE), Hand-Schüller-Christian disease, 233
RILEY, HARRIS D., JR. (WITH WARNER, CHARLES L., AND BRITT, ROBERT L.),

Bronchopulmonary sequestration in infancy and childhood, 521

ROGERSON, ALEXANDER G. (WITH JONES, MALCOLM D., AND SAKAI, HSAJIQ), Intravenous cholangiography in children with fibrocystic disease of the pancreas, 172

ROMAN, LIWANAG P., AND MIDDELKAMP, J. NEAL, Narcotic addiction in a newborn infant, 231

ROMINGER, C. JULES (WITH CANTLIN, M. L., AND O'SULLIVAN, WARD D.), Surgical treatment of some pulmonary conditions in childhood, 432

ROSS, DONALD C., An experiment in teaching comprehensive pediatrics, 336

RUBIN, ALAN, AND MURPHY, DOUGLAS P., Studies in human reproduction. III. The frequency of congenital malformations in the offspring of nondiabetic and diabetic individuals, 579

S

SAKAI, HSAJIQ (WITH JONES, MALCOLM D., AND ROGERSON, ALEXANDER G.), Intravenous cholangiography in children with fibrocystic disease of the pancreas, 172

SCHERZ, ROBERT G., AND GEPPERT, LEO J., Recognition and treatment of adrenal crises in the newborn infant, 645

SENZ, EDWARD H., A terminology and differential diagnosis for brief seizures in infants and children; and the definition of petit mal, 441

—, AND GOLDFARB, DONALD L., Coma in a child following use of isopropyl alcohol in sponging, 322

SHARP, J. D., Correspondence, 254

SHEFFIELD, JAMES A. (WITH JABBOUR, J. T., AND MONTALVO, J. M.), Severe neurological manifestations in four children receiving Compazine (prochlorperazine), 153

SKANDALAKIS, JOHN E. (WITH LIONAKIS, BASIL, GRAY, STEPHEN W., AND HOPKINS, W. A.), Empyema in children, 719

SLEDGE, WINNIE L. (WITH KAMIN, SHELDON H., AND LLEWELLEYN, CHARLEY JACKSON), Group dynamics in the treatment of epilepsy, 410

SMITH, NANCY (WITH WHEELER, JAMES E., PLOTKIN, ROBERT F., AND FROMME, DALORES), Acute upper respiratory disease: clinical and bacteriological response to short-term treatment with penicillin V, 571

SMITH, NATHAN J., Iron as a therapeutic agent in pediatric practice, 37

SOLOMONS, BETHEL, The history of infant welfare, 360

SPARACO, ROSE (WITH WAGNER, RICHARD, AND MEYERRIECKS, NORMA), Glycogen storage disease, 683

STADLER, HAROLD E., Familial dysautonomia, 481

STICKLER, GUNNAR B., AND PINKEL, DONALD, Calculation of nutritional allowances for infants and children on the basis of body surface, 464

STILES, FRANK C., Coproliths (calcified appendiceal calculi) in children, 741

T

TALLERMAN, KENNETH H., Correspondence, 252

THANNISCH, GEORGE, Multiple hepatic abscesses due to Ascaris lumbricoides, 602

THELANDER, H. E., PHELPS, JANE K., AND KIRK, E. WALTON, Learning disabilities associated with lesser brain damage, 405

— (WITH GERHARD, A. M.), Cerebral angiomatosis, 586

THURSTON, DON L. (WITH HOLOWACH, JEAN), A clinical evaluation of acetazolamide (Diamox) in the treatment of epilepsy in children, 160

TOMSOVIC, EDWARD J., AND JAVID, HUSHANG, Cicatricial stenosis of the esophagus following ingestion of a single urine-sugar reagent tablet, 608

— (WITH GRAVEN, STANLEY N.), Celiac disease: response to a gluten-free diet, 726

TURNER, J. A. P. (WITH EHRLICH, R. M., AND CLARKE, MAIRIN), Neonatal varicella, 139

V

VERHULST, HENRY L. (WITH CANN, HOWARD M.), The salicylate problem with special reference to methyl salicylate), 271

VIGNEC, ALFRED J., The role of Candida albicans in the common skin disorders of infancy and early childhood, 692

VOGEL, EDWARD H., JR. (WITH FAIRCHILD, JOHN P., GRABER, CHARLES D., AND INGERSOLL, ROBERT L.), Flora of the umbilical stump, 538

W

WADLINGTON, WILLIAM B., Familial trembling of the chin, 316

WAGNER, RICHARD, MEYERRIECKS, NORMA, AND SPARACO, ROSE, Glycogen storage disease, 683

WARNER, CHARLES L., BRITT, ROBERT L., AND RILEY, HARRIS D., JR., Bronchopulmonary sequestration in infancy and childhood, 521

WHEELER, JAMES E., PLOTKIN, ROBERT F., FROMME, DALORES, AND SMITH, NANCY, Acute upper respiratory disease: clinical and bacteriological response to short-term treatment with penicillin V, 571

WHITE, PARK JERAULD, Correspondence, 506

Y

YANET, HERMAN, Multiple handicaps in the cerebral palsied, 639

SUBJECT INDEX*

A

Acetazolamide (Diamox) in treatment of epilepsy in children, clinical evaluation of (Holowach and Thurston), 160
Adenocarcinoma of thyroid, papillary (CPC), 494
Adenovirus pneumonia (Blattner), 631
Adrenal crises in newborn infant, recognition and treatment (Scherz and Geppert), 645
  hormonal drugs in pediatric practice (Bongiovanni et al.), 3
  hyperplasia, congenital virilizing, adrenogenital syndrome due to (Etteldorf et al.), 389
Adrenogenital syndrome due to congenital virilizing adrenal hyperplasia (Etteldorf et al.), 389
Amino acids, serum and urine, in infantile toxicosis (Choremis and Nicolopoulos), 515
Angiomatosis, cerebral (Gerhard and Thelander), 586
Anorexia, treatment of (MacKenzie), 187
Antibacterial agents, pediatric use of (Kempe), 19
Arachnidism, necrotic (Blattner), 377
Ardmore disease, new clinical entity (Blattner), 249
Ascaris lumbricoides, multiple hepatic abscesses due to (Thannisch), 602
Asian influenza, neurologic complications of (Blattner), 751

B

Bacteriological diagnosis of childhood tuberculosis using bone marrow and peripheral blood aspirates (Kimsey), 413
Basic research program (editorial), 388
Behavior disorders in children, deanol in treatment of (Oettinger), 671
Bilirubin, serum, levels in newborn infant, and their relation to clinical icterus and liver function studies (Bogin et al.), 529
Blood aspirates, peripheral, and bone marrow in bacteriological diagnosis of childhood tuberculosis (Kimsey), 413
Body surface, calculation of nutritional allowances for infants and children on basis of (Stickler and Pinkel), 464
Bone marrow and peripheral blood aspirates in bacteriological diagnosis of childhood tuberculosis (Kimsey), 413
Books:
  Affections non congénitales de l'anus et du rectum chez l'enfant (Duhamel), 386
  Anthropology and human nature (Montagu), 137
  Antisera, toxoids, vaccines and tuberculins in prophylaxis and treatment (Parish), 759
  Atomic age and our biological future (Brondsted), 759
  Care of the well and the sick child (Catel), 137
  Child care and training (Faegre et al.), 257
  Chirurgie infantile d'urgence (Fèvre), 758
  Chirurgie préventive du la tuberculose ostéo-articulaire (Kaufmann), 386
  Cleft palate and speech (Morley), 512
  Clinical and immunologic aspects of fungous diseases (Wilson), 136
  Common sense about gifted children (Abraham), 511
  Congenital anomalies of the hand and their surgical treatment (Barsky), 759
  Directory for exceptional children, 386
  Drugs; their nature, action and use (Beckman), 256
  Emotional problems of adolescents (Gallagher and Harris), 510
  Epilepsy handbook (Gibbs and Stamps), 757
  Essentials of pediatrics (Jeans et al.), 760
  Étude radiologique de la circulation veineuse du membre supérieur (sujet normal) (Lavizzari and Ottolini), 512
  Growth and development of the young child (Breckenridge and Murphy), 257
  Guide to summer camps and summer schools, 760
  Handbook of treatment of acute poisoning (Bensley and Joron), 760
  Human blood in New York City, 758
  l'Hydrocephalie du nourrisson (Klein), 386
  Laboratory medicine-hematology (Miale), 757
  Medical assistant (Bredow), 512
  Modern prescription drugs: their impact on the family budget, 759

*July, pp. 1-138; August, pp. 139-258; September, pp. 259-388; October, pp. 389-514; November, pp. 515-644; December, pp. 645-776

Books—Cont'd
Nursing of mental defectives (Hallas), 760
Nursing mother (Richardson), 758
Orthopedics for the general practitioner (Kenney and Larson), 257
Our nuclear adventure (Arnott), 512
Paediatrics for nurses (Watkins), 760
Parents' guide to everyday problems of boys and girls (Gruenberg), 386
Pediatric gynecology (Schauffler), 760
Pediatric surgery (Swenson), 756
Pharmacologic principles of medical practice (Krantz and Carr), 257
Practical cardiology (Hyman), 760
Primer of cerebral palsy (Russ and Soboloff), 760
Principles of internal medicine (Harrison), 760
Psychology of medical practice (Hollender), 638
Régimes du nourrisson, bien-portant ou malade (Delthil), 257
Rehabilitation of the cardiovascular patient (White et al.), 511
Signs, symptoms and treatment of certain acute intoxications (Deichmann and Gerarde), 386
Sinusites de l'enfance (Terracol and Guerrier), 759
Surgery in infancy and childhood (White and Dennison), 511
Tuberculosis in white and Negro children. Volume I. Roentgenologic aspects of The Harriet Lane Study (Hardy), 637
Volume II. Epidemiologic aspects of The Harriet Lane Study (Brailey), 637
Brain damage, lesser, learning disabilities associated with (Thelander et al.), 405
Bronchopulmonary sequestration in infancy and childhood (Warner et al.), 521

C

Candida albicans, role in common skin disorders of infancy and early childhood (Vignec), 692
Cardiac failure in newborn infant, cerebral arteriovenous fistula producing, 731
Catheterization, right heart, in infants and children (Fink et al.), 566
Celiac disease: response to gluten-free diet (Graven and Tomsovic), 726
Cerebral angiomatosis (Gerhard and Thelander), 586
arteriovenous fistula producing cardiac failure in newborn infant (Pollock and Laslett), 731
palsied children, education of (Katz), 467
Chin, familial trembling of (Wadlington), 316
Cholangiography, intravenous, in children with fibrocystic disease of pancreas (Jones et al.), 172
Clinical Pathological Conferences:
congenital muscular dystrophy, 744
Hashimoto's thyroiditis, 494
hypertrophic interstitial neuritis (Déjerine-Sottas disease), 107
leukemia with cerebral complications, 349
papillary adenocarcinoma of thyroid, 494
pulmonary hypertension, 615
sepsis of newborn, 241
Coma in child following use of isopropyl alcohol in sponging (Senz and Goldfarb), 322
Comments on Current Literature:
adenovirus pneumonia, 631
Ardmore disease, new clinical entity, 249
environmental penicillin and penicillin-resistant Staphylococcus aureus, 131
mammalian viruses and rickettsiae; new methods of purification and recovery, 503
necrotic arachnidism, 377
neurologic complications of Asian influenza, 751
Compazine (prochlorperazine), severe neurological manifestations in four children receiving (Jabbour et al.), 153
Congenital malformations, frequency of, in offspring of nondiabetic and diabetic individuals; studies in human reproduction, III (Rubin and Murphy), 579
Coproliths (calcified appendiceal calculi) in children (Stiles), 741
Correspondence, 252, 381, 506, 635

D

Deanol in treatment of disorders of behavior in children (Oettinger), 671
Déjerine-Sottas disease (CPC), 107
Dermal fistulas of dental origin in children (Olmsted), 221
Diabetes mellitus in infancy (Assevero and Moss), 227
Duodenal ulcer, perforated, in infant (Oeconomopoulos), 324

E

Eczema, allergic versus seborrheic infantile, treatment of (Crawford), 99
Editorial comments on therapeutic issue (Etteldorf), 1
Editor's Column:
basic research program, 388
hail and farewell, 761
Journal educational lectureships for 1958, 138
medical litany, 258
pet peeves, 387
tranquilizers, 764
visiting policies for children's hospitals, 513
Empyema in children (Lionakis et al.), 719
Encephalitis, influenza (Mellman), 292

Eosinophil level, circulating, in newborn infant following normal and difficult labor (Khalil), 662
Epilepsy in children, clinical evaluation of acetazolamide (Diamox) in treatment of (Holowach and Thurston), 160
group dynamics in treatment of (Kamin et al.), 410
terminology and differential diagnosis for brief seizures in infants and children; and definition of petit mal (Senz), 441
Epileptic child, treatment of (Hughes and Jabbour), 66
Esophagus, cicatricial stenosis of, following ingestion of single urine-sugar reagent tablet (Tomsovic and Javid), 608

F

Familial dysautonomia (Stadler), 481
trembling of chin (Wadlington), 316
Ferrous sulfate poisoning (Amerman et al.), 476
Fibrocystic disease of pancreas, intravenous cholangiography in children with (Jones et al.), 172
Fistulas, dermal, of dental origin, in children (Olmsted), 221
Flora of umbilical stump (Fairchild et al.), 538

G

Gastroenteritis, acute (Armstrong), 704
Gluten-free diet, response of celiac disease to (Graven and Tomsovic), 726
Glycogen storage disease (Wagner et al.), 683
Group dynamics in treatment of epilepsy (Kamin et al.), 410

H

Hail and farewell (editorial), 761
Hand-Schüller-Christian disease (Abbassy), 233
Hashimoto's thyroiditis (CPC), 494
Heart catheterization, right, in infants and children (Fink et al.), 566
Helmholz, Henry Frederic: in memoriam, 634
Hepatic abscesses, multiple, due to Ascaris lumbricoides (Thannisch), 602
Hydramnios as signal to physician responsible for newborn infants (DeYoung), 277
Hypertension, pulmonary (CPC), 615
Hypertrophic interstitial neuritis (Déjerine-Sottas disease) (CPC), 107

I

Icterus, clinical, and liver function studies, serum bilirubin levels in newborn infant and their relation to (Bogin et al.), 529
Immunization methods and materials (Batson and Christie), 51
In memoriam: Henry Frederic Helmholz, 634
Indian reservation, American, medicine at (Bush), 622
Infancy and childhood, bronchopulmonary sequestration in (Warner et al.), 521
and early childhood, role of Candida albicans in common skin disorders of (Vignec), 692
Infant welfare, history of (Solomons), 360
Infantile toxicosis, serum and urine amino acids in (Choremis and Nicolopoulos), 515
Infants and children, right heart catheterization in (Fink et al.), 566
Influenza, Asian, neurologic complications of (Blattner), 751
encephalitis (Mellman), 292
Inguinal hernia, incarceration of Meckel's diverticulum in (Kline), 479
Intestinal parasites, management of (Jung), 89
strangulation obstruction in newborn infant, methemoglobinemia associated with (Quillian et al.), 737
Iron as therapeutic agent in pediatric practice (Smith), 37
Isopropyl alcohol in sponging, coma in child following use of (Senz and Goldfarb), 322

J

Journal educational lectureships for 1958 (editorial), 138

K

Kidney disease, multicystic, unilateral (Coppridge and Ratliff), 330

L

Lead encephalopathy, subsequent mental development of children with, as related to type of treatment (Bradley and Baumgartner), 311
Learning disabilities associated with lesser brain damage (Thelander et al.), 405
Legg-Perthes disease, prognosis in (Broder), 451
Leptomeningitis due to Gaffkya tetragena (Perou et al.), 484
Leukemia with cerebral complications (CPC), 349
chronic monocytic, in childhood (Pearson and Diamond), 259
Liver function studies, clinical icterus and, serum bilirubin levels in newborn infant and their relation to (Bogin et al.), 529

M

Meckel's diverticulum, incarceration of, in inguinal hernia (Kline), 479
rupture of, in newborn infant, meconium peritonitis caused by (Gilbert and Rainey), 597
Meconium peritonitis caused by rupture of Meckel's diverticulum in newborn infant (Gilbert and Rainey), 597
Medical Progress:
history of infant welfare (Solomons), 360
obesity (Illingworth), 117
Mental development, subsequent, of children with lead encephalopathy as related to type of treatment (Bradley and Baumgartner), 311
Methemoglobinemia associated with intestinal strangulation obstruction in newborn infant (Quillian et al.), 737
Monocytic leukemia, chronic, in childhood (Pearson and Diamond), 259
Multicystic kidney disease, unilateral (Coppridge and Ratliff), 330
Muscular dystrophy, congenital (CPC), 744
Myofascial pain in childhood (Bates and Grunwaldt), 198

N

Narcotic addiction in newborn infant (Roman and Middelkamp), 231
Neonatal varicella (Ehrlich et al.), 139
Neurologic complications of Asian influenza (Blattner), 751
Newborn infant, cerebral arteriovenous fistula producing cardiac failure in (Pollock and Laslett), 731
circulating eosinophil level in, following normal and difficult labor (Khalil), 662
endotracheal aspirate of; studies on pH of respiratory tract (Jacobs and Papperman), 298
hydramnios as signal to physician responsible for (DeYoung), 277
meconium peritonitis caused by rupture of Meckel's diverticulum in (Gilbert and Rainey), 597
methemoglobinemia associated with intestinal strangulation in (Quillian et al.), 737
narcotic addiction in (Roman and Middelkamp), 231
recognition and treatment of adrenal crises in (Scherz and Geppert), 645
sepsis of (CPC), 241
serum bilirubin levels in, and their relation to clinical icterus and liver function studies (Bogin et al.), 529
vaccination against pertussis (Martin Du Pan), 180
News and notes, 135, 254, 382, 508, 635, 754
Nutritional allowances for infants and children on basis of body surface, calculation of (Stickler and Pinkel), 464

O

Obesity (Illingworth), 117
Oleandomycin, laboratory and clinical evaluation of (Koch and Asay), 676

P

Papillary adenocarcinoma of thyroid (CPC), 494
Pediatrics, comprehensive, experiment in teaching (Ross), 336
Penicillin and penicillin-resistant Staphylococcus aureus, environmental (Blattner), 131
V, clinical and bacteriological response to short-term treatment with, in acute respiratory disease (Wheeler et al.), 571
Peritonitis, meconium, caused by rupture of Meckel's diverticulum in newborn infant (Gilbert and Rainey), 597
Pertussis, vaccination of newborn infant against (Martin Du Pan), 180
Pet peeves (editorial), 387
Poisoning: cicatricial stenosis of esophagus following ingestion of single urine-sugar reagent tablet (Tomsovic and Javid), 608
coma in child following use of isopropyl alcohol in sponging (Senz and Goldfarb), 322
ferrous sulfate (Amerman et al.), 476
Prochlorperazine, severe neurological manifestations in four children receiving (Jabbour et al.), 153
treatment of nausea and vomiting in children with (Daeschner et al.), 148
Pulmonary conditions in childhood, surgical treatment of (Cantlin et al.), 432
hypertension (CPC), 615

R

Reproduction, human, studies in, III; frequency of congenital malformations in offspring of nondiabetic and diabetic individuals (Rubin and Murphy), 579
Respiratory disease, acute upper; clinical and bacteriological response to short-term treatment with penicillin V (Wheeler et al.), 571
tract, studies on pH of: I. endotracheal aspirate of healthy newborn infants (Jacobs and Papperman), 298
Rheumatic pneumonitis, Part II; report on clinical and laboratory findings in twenty-three patients (Goldring et al.), 547
Rickettsiae, viruses and, mammalian; new methods of purification and recovery (Blattner), 503
Rocky Mountain spotted fever in children (Missirliu et al.), 303

S

Sacrococcygeal teratoma, malignant, case of (McConnell), 489
Salicylate problem with special reference to methyl salicylate (Cann and Verhulst), 271
Schizophrenia, childhood, toe walking in (Colbert and Koegler), 219
Sepsis of newborn (CPC), 241
Sequestration, bronchopulmonary, in infancy and childhood (Warner et al.), 521
Skin disorders, common, of infancy and early childhood, role of Candida albicans in (Vignec), 692
Special article: medicine at American Indian reservation (Bush), 622
Stenosis, cicatricial, of esophagus, following ingestion of single urine-sugar reagent tablet (Tomsovic and Javid), 608
Surgical treatment of pulmonary conditions in childhood (Cantlin et al.), 432

T

Tachycardia, supraventricular, simulating ventricular paroxysmal tachycardia in infancy (Castellanos et al.), 285
Teaching comprehensive pediatrics, experiment in (Ross), 336
Teratoma, malignant sacrococcygeal, case of (McConnell), 489
Therapeutic issue, 1-106
Thyroid, papillary adenocarcinoma of (CPC), 494
Thyroiditis, Hashimoto's (CPC), 494
Toe walking in childhood schizophrenia (Colbert and Koegler), 219
Toxicosis, infantile, serum and urine amino acids in (Choremis and Nicolopoulos), 515
Tranquilizers (editorial), 764
Trigonal mucosa, prolapsing, in infant (Espinosa et al.), 446
Tuberculosis, childhood, bacteriological diagnosis using bone marrow and peripheral blood aspirates (Kimsey), 413

U

Umbilical stump, flora of (Fairchild et al.), 538

V

Vaccination of newborn infant against pertussis (Martin Du Pan), 180
Vaginitis, pediatric, microbiological study of (Kotcher et al.), 210
Varicella, neonatal (Ehrlich et al.), 139
Viruses and rickettsiae, mammalian; new methods of purification and recovery (Blattner), 503
Visiting policies for children's hospitals (editorial), 513
Vomiting, nausea and, in children, treatment with prochlorperazine (Daeschner et al.), 148

INDEX NUMBER

Vol. 53 DECEMBER, 1958 No. 6

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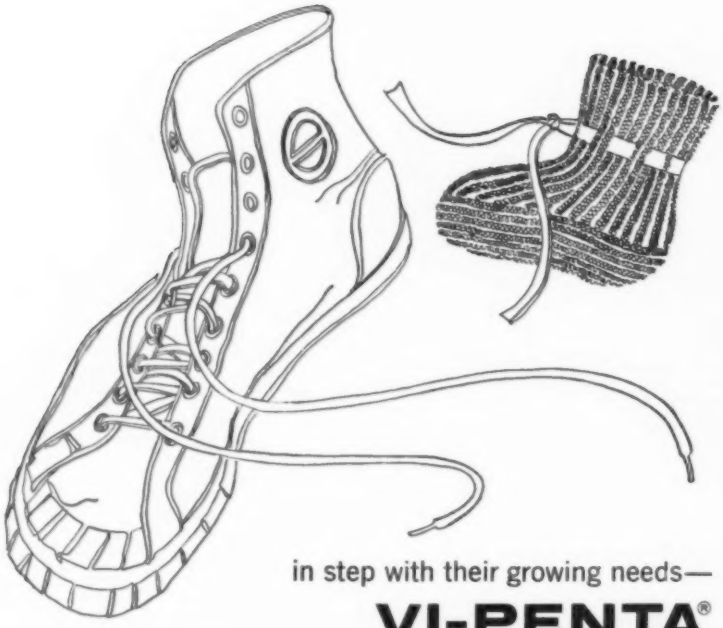
Table of Contents on 3rd Cover



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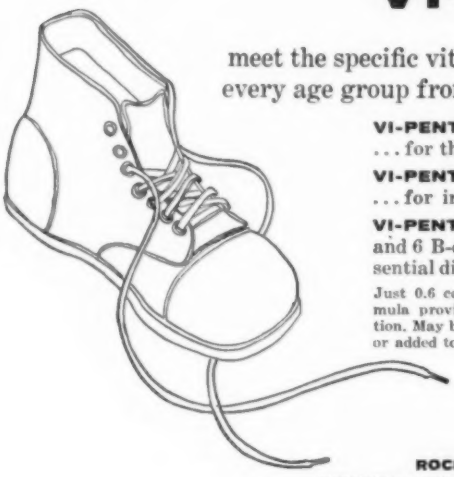

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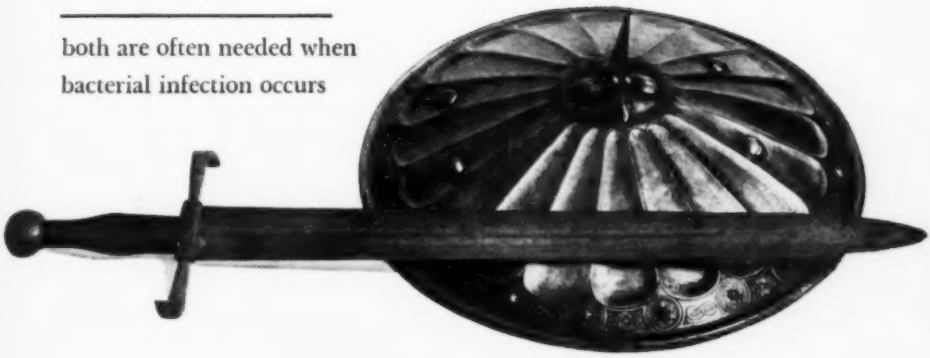

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ACTIVITY OF SERUM ALDOLASE AND LACTIC DEHYDROGENASE IN PATIENTS AFFECTED WITH DUCHENNE MUSCULAR DYSTROPHY AND IN THEIR IMMEDIATE RELATIVES.
By Hubert C. Soltan, B.A., and Marcel C. Blanchaer, B.A., M.D., C.M.

COMPARISON OF INTRAMUSCULAR IRON-DEXTRAN AND ORAL FERROUS SULFATE IN THE TREATMENT OF IRON-DEFICIENCY ANEMIA.
By Wei Liang Yu, M.D., Kariagownder Manonmani, M.D., and R. Janet Watson, M.D., Brooklyn, N. Y.

CONGENITAL CHOANAL ATRESIA.
By Irving Weinstock, M.D., Brooklyn, N. Y.

ANHIDROTIC ECTODERMAL DYSPLASIA: USE OF THE SILVER NITRATE PLATE TO DETECT ANHIDROSIS.
By Lucille B. Glicklich, M.D., and Ira M. Rosenthal, M.D., Chicago, Ill.

RHEUMATIC PNEUMONITIS: PATHOLOGIC FEATURES.
By R. Foster Scott, M.D., Wilbur A. Thomas, M.D., and J. M. Kissane, M.D., St. Louis, Mo.

FOREIGN BODIES IN THE VAGINA OF CHILDREN.
By J. Philip Ambuel, M.D., Columbus, Ohio.

PEDIATRIC EMPYEMA: A SECOND LOOK AT ITS INCIDENCE AND IMPORTANCE.
By William B. Kiesewetter, M.D., Joseph R. Rusnock, M.D., and Bertram R. Girdany, M.D., Pittsburgh, Pa.

ANOMALOUS COURSE OF LEFT PULMONARY ARTERY: A CAUSE OF OBSTRUCTIVE EMPHYSEMA IN INFANTS.
By Frank E. Sherman, M.D., Pittsburgh, Pa.

NEONATAL OMPHALITIS AND PYELONEPHRITIS.
By William E. Delaney III, M.D., Philadelphia, Pa.

VARICELLA GANGRENOSA.
By Albert M. Crocker, M.D., and J. Neal Middelkamp, M.D., St. Louis, Mo.

INTERSCORER AGREEMENT FOR THE GRAHAM BEHAVIOR TEST FOR NEONATES.
By Judy F. Rosenblith, Ph.D., and Lewis P. Lipsitt, Ph.D., Providence, R. I.

ADVANTAGES OF FLOATING LIPIODOL AS A FURTHER TEST FOR VOIDING EFFICIENCY.
By Myron S. Roberts, M.D., and John K. Lattimer, M.D., New York, N. Y.

THE ANTIBIOTIC PROPHYLAXIS OF BACTERIAL COMPLICATIONS OF MEASLES.
By Samuel Karelitz, M.D., and Henry D. Isenberg, M.D., New Hyde Park, N. Y.

THE MYXEDEMA REFLEX IN INFANTS AND CHILDREN WITH HYPOTHYROIDISM.
By C. Y. Bowers, M.D., Douglas L. Gordon, M.D., and Albert Segaloff, M.D., New Orleans, La.

THE RELATIONSHIP BETWEEN "MIXED DOMINANCE" AND READING DISABILITIES.
By Robert L. Spitzer, M.D., Richard Rabkin, M.D., and Yale Kramer, M.D., New York, N. Y.

CONGENITAL INTERRUPTION OF THE AORTIC ARCH.
By Paul G. Quie, M.D., Rosalind Novick, M.D., Paul Adams, Jr., M.D., Ray C. Anderson, Ph.D., M.D., and Richard L. Varco, Ph.D., M.D., Minneapolis, Minn.

THE PROTEIN REQUIREMENT OF INFANTS.
By L. Emmett Holt, Jr., M.D., New York, N. Y.

JUVENILE XANTHOGRANULOMA WITH OCULAR INVOLVEMENT.
By Reza Gharib, M.D., Edmund C. Burke, M.D., and Louis A. Brunsting, M.D., Rochester, Minn.

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1. New and Unused Therapeutics Committee, Am. Coll. Allergists: Ann. Allergy 16:237 (May-June) 1958. 2. Spielman, A. D.: Ibid. p. 242. 3. Idem: New York J. Med. 57:3329 (Oct. 15) 1957.

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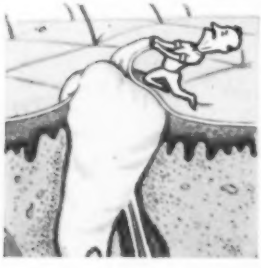

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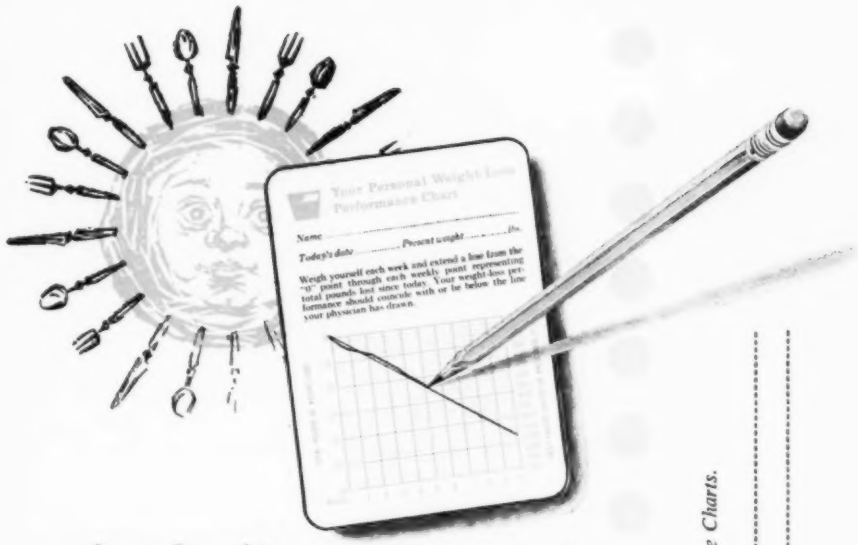
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1. Spielman, A. D.: New York J. Med. *55*:1603 (June 1) 1955.
2. Shinefield, M. A.: New York J. Med. *56*:1466 (May 1) 1956.
3. Dalven, J., and Romano, F. J.: New York J. Med. *57*:1748 (May 15) 1957.
4. Gundy, J. E.: J. Pediat. *51*:516 (Nov.) 1957.
5. Spielman, A. D.: A.M.A. Arch. Otolaryng. *67*:204 (Feb.) 1958.

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WHY COLLOID BATHS FOR THE ECZEMAS?

The pruritus of eczema, and particularly of atopic dermatitis, is possibly as severe as any that will be encountered in pediatric practice.[1] Exacerbation or infection of lesions by scratching is so common that restraints are often necessary.

Local hydrocortisone has not been found to be of measurable value for relief of itching.[2] A similar criticism has been made of topical antihistamines, which are also "highly sensitizing."[3] Overtreatment dermatitis may occur as a result of a multiplicity of topically applied drugs,[1] and systemic toxic reactions may result from drugs applied over a large area, particularly in the infant. A rebound phenomenon is often observed after stoppage of steroid medication, with a renewal of the eczema that is more acute than the original case.[4] Finally, suppression of adrenal function by systemic steroid therapy is no small problem.[5-8]

Considering these and other factors, colloid bath therapy is increasingly used as a safe and effective adjunct to the total therapy of the eczemas. Regarding allergic infantile eczema, Crawford[9] states: "Colloid baths relieve the itching for short periods of time and are most useful before bedtime . . . A good commercial oatmeal preparation is Aveeno." In acute atopic dermatitis, Senear and Haeberlin[10] consider Aveeno Colloid Baths to be "very useful as basic wet therapy." A good rule-of-thumb, according to these authors, is "*the wetter the inflammation, the wetter the treatment* . . . for in the presence of exudation of the skin most applications except wet ones are floated away and they either do nothing or aggravate the condition."

A companion product to Aveeno Colloidal Oatmeal is Aveeno "Oilated." This product contains, in addition to colloidal oatmeal, 35% oils for extra emolliency. Aveeno "Oilated" colloidal *emollient* baths are indicated in dry, chronic dermatoses where additional softening and lubricating effects are desired . . . and to offset the discomfort of crusting and scaling.

TWO TYPES OF COLLOID BATHS FOR ALL STAGES OF THE ECZEMAS

. . . for acute, inflamed skin
AVEENO® Colloidal Oatmeal
Available in 18 oz. and 4 lb. boxes

. . . for dry, chronic skin
AVEENO® "OILATED"
Available in 10 oz. cans.

References: 1. Sternberg, T.H. and Newcomer, V.D.: Am. Pract. & Digest. Treat. 6:1102(July) 1955. 2. Robin, M. and Kopecs, J.G.: J. Invest. Dermat. 29:91(Aug.) 1957. 3. Leider, M. Practical Pediatric Dermatology. St. Louis, C. V. Mosby Company, 1956, p. 210. 4. Bookman, R.: J.A.M.A. 159:1275(Nov. 26) 1955. 5. Nicholas, J.A., et al.: J.A.M.A. 164:261, 1956. 6. Breed, E.S.: M. Clin. North America, May 1957. 7. Howland, W.S., et al.: J.A.M.A. 160:1271, 1956. 8. Salassa, R.M. et al.: J.A.M.A. 152:1509, 1953. 9. Crawford, L.V.: J. Pediatrics 53:99(July) 1958. 10. Senear, F.E. and Haeberlin, J.B., Jr.: in M. Clin. North America, March 1958. Philadelphia, W. B. Saunders Company, 1958, pp. 489-496. 11. Dick, L.A.: To be published.

AVEENO CORPORATION 250 West 57th Street New York 19, N. Y.

put
out the
fire
of
DIAPER SCALD*
with
AVEENO OINTMENT

(the soothing colloidal oatmeal ointment)

*highly inflamed, weeping diaper rash

Soothing

Ten years of clinical experience and an extensive bibliography have established the value of Aveeno Colloidal Oatmeal as a protective antipruritic and soothing agent for inflamed skin.[1-4]

Absorbent

The excellent absorbent quality of the colloidal oatmeal in Aveeno Ointment helps remove irritating exudates from the skin and promotes healing even in severe cases of diaper rash.

Antibacterial

Hexachlorophene effectively inhibits the growth of B. Ammoniagenes . . . the major cause of ammoniacal diaper rash.

Protective

Aveeno Ointment provides both the protective benefits of a paste and the soft, creamy properties of an ointment.

Other Indications: Itching or irritated skin conditions where soothing protection is desired — chafing, rectal itching, exanthems, non-specific dermatoses.

Active Ingredients: Aveeno® Colloidal Oatmeal, zinc oxide, and hexachlorophene (0.5%) in an emollient base.

Available in 1 oz. and 4 oz. tubes.

References: 1. Senear, F. E., and Haeberlin, J. B., Jr.: in M. Clin. North America, March 1958. Philadelphia, W. B. Saunders Company, 1958, pp. 489-496. 2. Crawford, L. V.: J. Pediatrics 53:99 (July) 1958. 3. Franks, A. G.: Am. Pract. & Digest Treat. (in press). 4. Smith, G. C.: J. South Carolina M. A. 54:282 (August) 1958.

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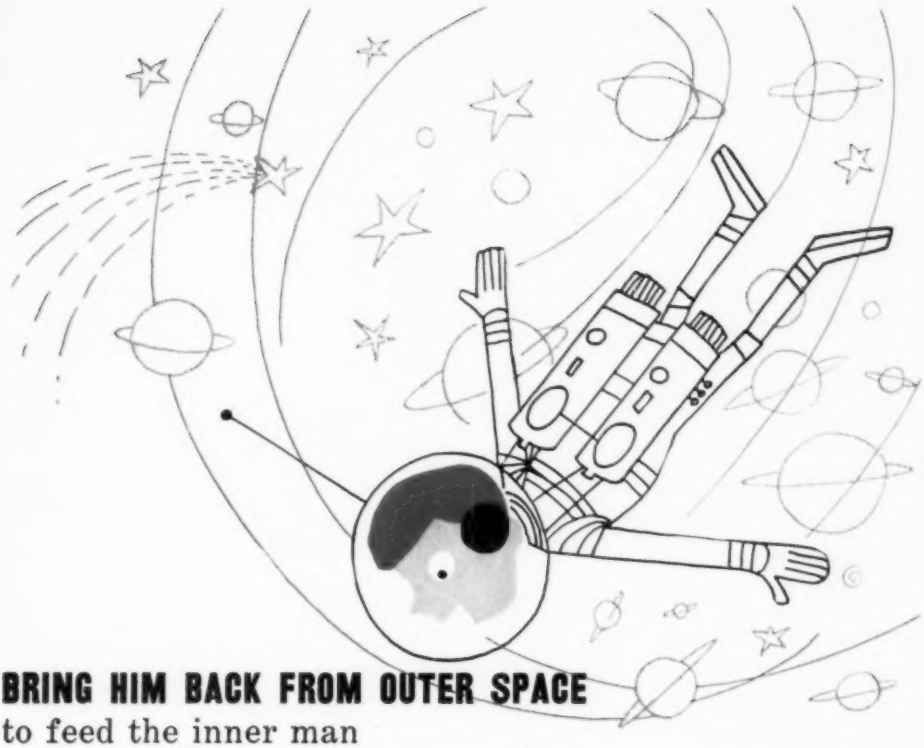
250 West 57th St., New York 19, N.Y.



BRING HIM BACK FROM OUTER SPACE
to feed the inner man

Anorectic space cadets zoom in for meals when REDISOL takes hold. This dietary supplement—Vitamin B_{12}—often stimulates appetite with consequent weight gain.

Soluble REDISOL Tablets (25, 50, 100, 250 mcg.) and cherry-flavored REDISOL Elixir (5 mcg. per 5 cc.) mix readily with liquids.

REDISOL is a trade-mark of Merck & Co., Inc.

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DIVISION OF MERCK & CO., Inc., PHILADELPHIA 1, PA.

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by A. Lewin-Funke

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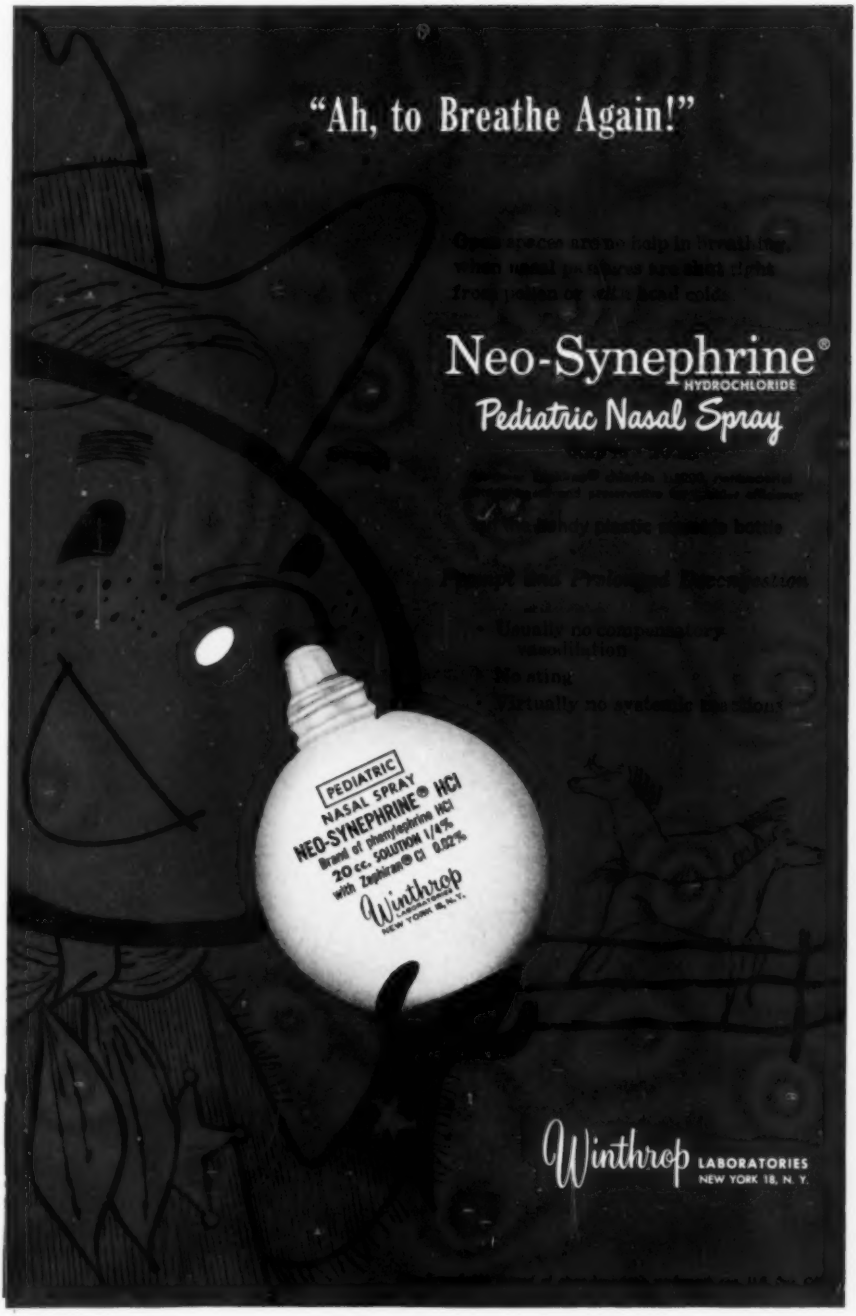
The Metropolitan Museum of Art

Classic therapy
for preventing and healing
diaper rash
excoriation, chafing, irritation

DESITIN®
OINTMENT

. . . enduring in its efficacy
. . . pleasing in its simplicity
. . . exemplifying pharmaceutical elegance

SAMPLES on request DESITIN CHEMICAL COMPANY
812 Branch Ave., Providence 4, R. I.


"Ah, to Breathe Again!"
Neo-Synephrine®
HYDROCHLORIDE
Pediatric Nasal Spray
PEDIATRIC
NASAL SPRAY
NEO-SYNEPHRINE® HCl
Brand of phenylephrine HCl
20 cc. SOLUTION 1/4%
with Zephiran® Cl 0.02%
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problem child?

Because irritability, excessive anger and failure to communicate adequately are often the first indications of emotional disorder in children, they are as important to treat as the more overt symptoms of physical disease. Serpasil provides a mild and selective shield against stress in the over-reactive, fearful, rebellious child. It frees him from tensions, helps him to eat and sleep better, makes him more amenable to parental guidance.

Serpasil®
(reserpine CIBA)

TABLETS, 1 mg. (scored), 0.25 mg. (scored) and 0.1 mg.
ELIXIRS, 1 mg. and 0.2 mg. per 4-ml. teaspoon.

CIBA
SUMMIT, N. J.

when all the fuss is about colds,
teething, postinoculation reactions,
pruritic conditions

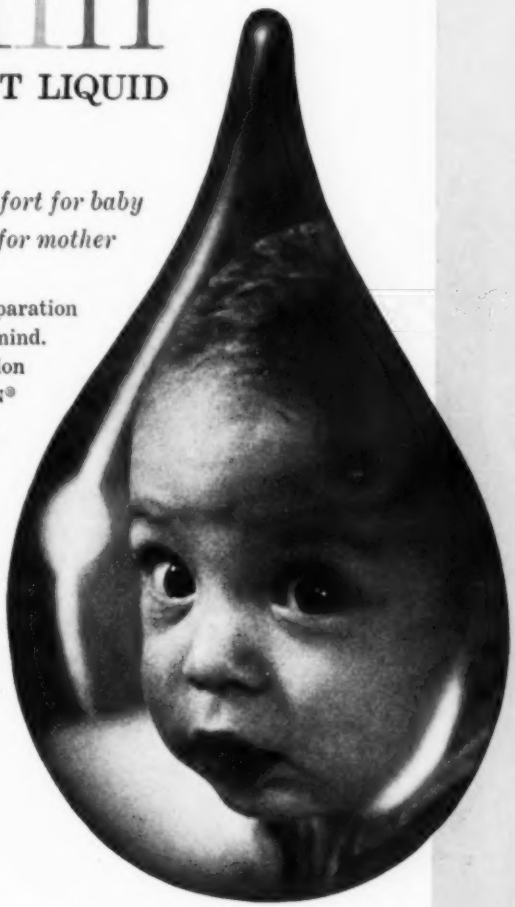
℞
NEW, dropper-administered

Corilin*

INFANT LIQUID

- *provides quick comfort for baby*
- *eliminates medication difficulties for mother*

Antihistaminic-analgesic-antipyretic preparation designed with *both* baby *and* mother in mind. Each cc. of raspberry-flavored solution contains 0.75 mg. CHLOR-TRIMETON® (chlorprophenpyridamine maleate), 80 mg. sodium salicylate and 25 mg. glycine. 30 cc. bottle with plastic calibrated dropper.



Schering

SCHERING CORPORATION
BLOOMFIELD, NEW JERSEY

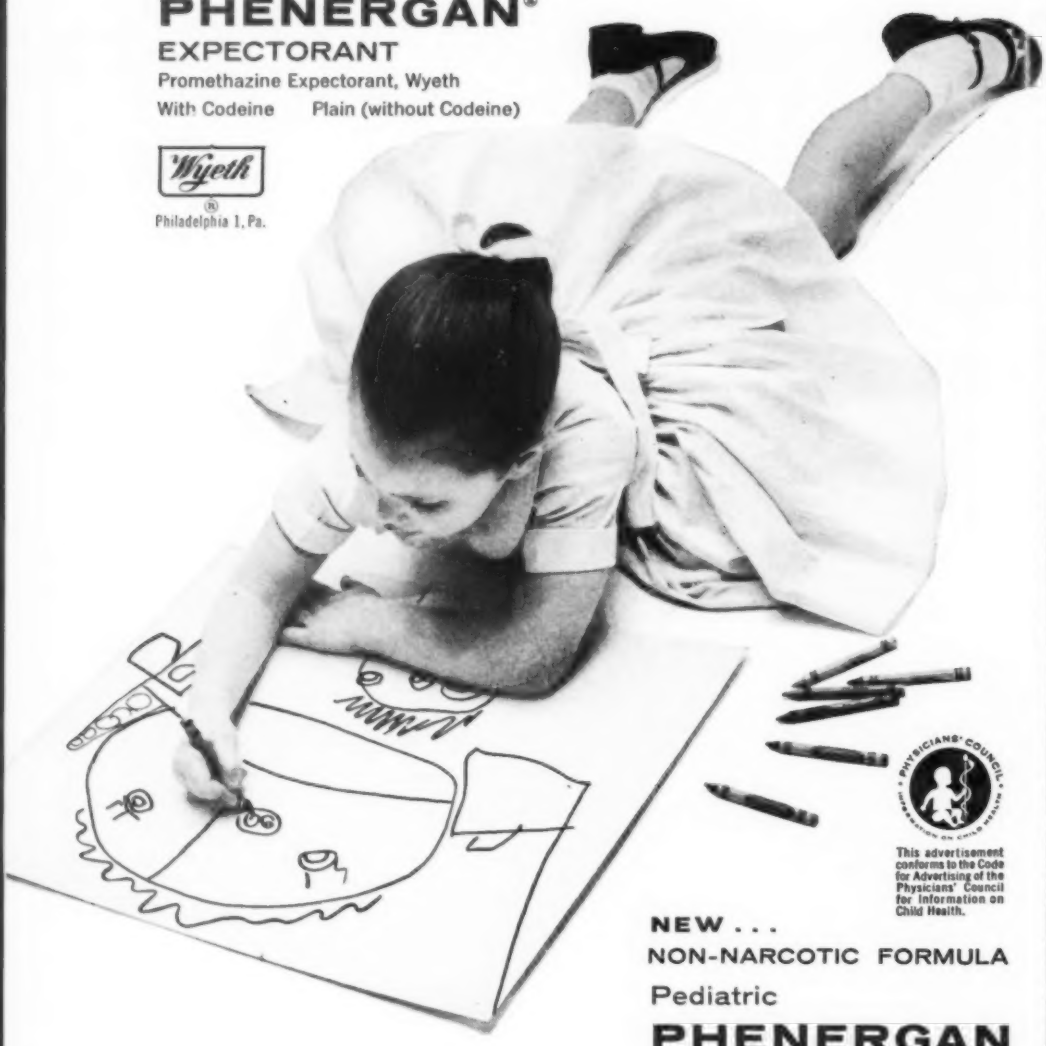
*T.M. CR-J-1108

to *quiet* the cough
and *calm* the patient

Expectorant action
Antihistaminic action
Sedative action
Topical anesthetic action

PHENERGAN®
EXPECTORANT
Promethazine Expectorant, Wyeth
With Codeine Plain (without Codeine)

Wyeth®
Philadelphia 1, Pa.



PHYSICIANS' COUNCIL ON CHILD HEALTH

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.

NEW . . .
NON-NARCOTIC FORMULA
Pediatric
PHENERGAN
EXPECTORANT
with Dextromethorphan*, Wyeth

*Dextromethorphan for an antitussive action equivalent to that of codeine without codeine's side-effects

In Post-Tonsillectomy care

"Post-operative pain...was decidedly decreased..."[1]

"...the incidence of bleeding was nil."[2]

"The tonsillar fossae...were uniformly cleaner..."[1]

Intermittent exercise of the pharyngeal muscles associated with the chewing of ORABIOTIC relieves postoperative discomfort, lessens difficulty in swallowing and stimulates increased salivary flow—thus keeping the oropharyngeal area moist and clean.

Patients receiving ORABIOTIC routinely after tonsillectomy were more comfortable and returned to a normal diet "within 3 to 5 days"[3] instead of the usual week to 10 days.

Orabiotic®

Antibiotic
Analgesic

CHEWING TROCHES

"A bacteriostatic bath" for the oropharynx

Each ORABIOTIC chewing gum troche contains:

Neomycin (from sulfate)	3.5 mg.
Gramicidin	0.25 mg.
Propesin (propyl p-aminobenzoate)	2.0 mg.

Dosage: One troche q.i.d. chewed for 10-15 minutes from the first through the fifth day after tonsillectomy. In other conditions, one troche q.i.d.

Supplied: In packages of 10 and 20.

White's

WHITE LABORATORIES, INC.
KENILWORTH, NEW JERSEY

References: 1. Rittenhouse, E. A.: Prevention of Secondary Hemorrhage in Tonsillectomy, E.E.N.T. Mo. 36:406 (July) 1957. 2. Fox, S. L.: Tonsillectomy and Adenoidectomy in Review, Clin. Med. 4:699 (June) 1957. 3. Granberry, C., and Beatrous, W. P.: Effect of a New Chewing Troche on Post-Tonsillectomy Morbidity, E.E.N.T. Mo. 36:294 (May) 1957.

in all diarrheas

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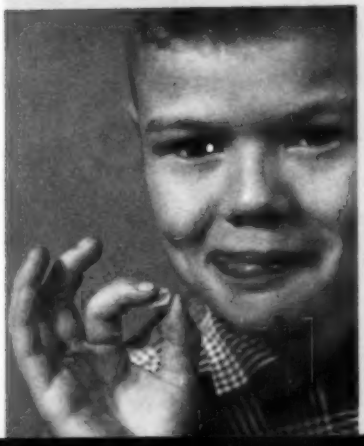
Now . . . in soluble tablets, too
. . . and they taste delicious



easier vitamin protection from
throughout the growth

new 'Vi-Sol' tablets

Symbol of vitamin protection

Tri-Vi-Sol®

3 basic vitamins

drops · tablets

Now, you can select the 'V

ction from infancy
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Sol® — *mins* — **blets**

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elect the 'Vi-Sol' vitamin level 3 VITAMINS 6 VITAMINS 10 VITAMINS *and form*

Your young patients will enjoy the delicious fruit-like flavors of the new 'Vi-Sol' tablets. Children take them by themselves—no need for messy teaspoons or swallowing with water.

Now . . . when you prescribe Tri-Vi-Sol, Poly-Vi-Sol or Deca-Vi-Sol, be sure to specify form: drops or tablets. New 'Vi-Sol' tablets are available in bottles of 24 and 100.

Your Mead Johnson Representative will be pleased to provide you with samples for your convenience in starting your patients on 'Vi-Sol' drops or tablets.

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for easier vitamin protection of infants and children

now . . . in soluble tablets too . . . and they taste delicious

Tri-Vi-Sol®	Poly-Vi-Sol®	Deca-Vi-Sol®
3 basic vitamins	*6 essential vitamins*	*10 significant vitamins*
drops · tablets	drops · tablets	drops · tablets

'Vi-Sol' tablets give you a new appealing dosage form for continuing vitamin protection of children.

3 out of 4 mothers who have children in the 'Vi-Sol' drops age have older children in the 'Vi-Sol' tablet age. These mothers will appreciate your prescription of easy-to-take 'Vi-Sol' tablets.

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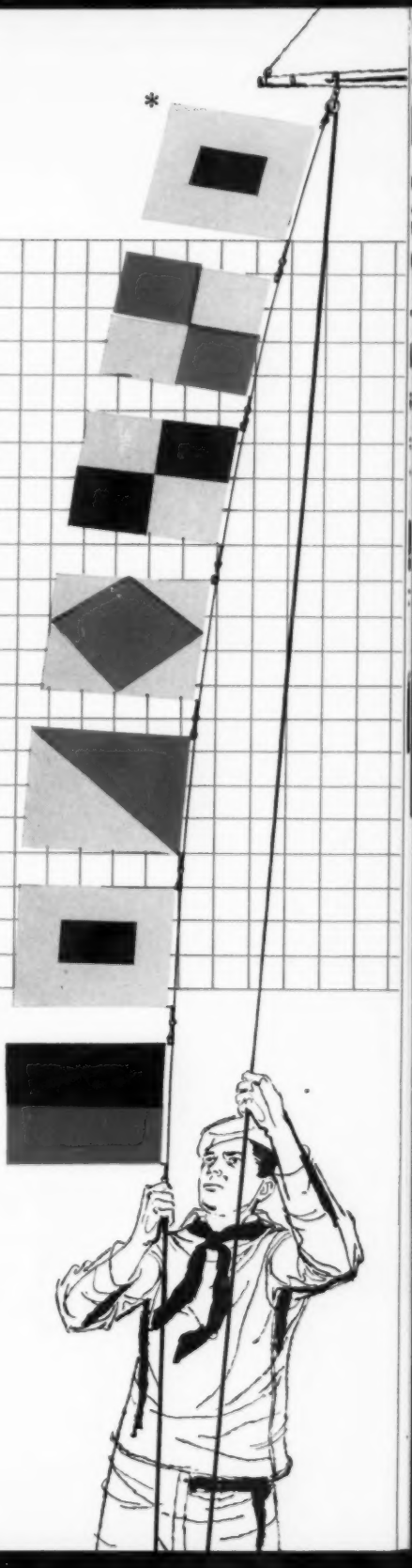
In urinary-tract infections

HIGH TISSUE LEVELS

HIGH BLOOD LEVELS

LOW TOXICITY



***International Code flags spelling SULFOSE.**

SUSPENSION TABLETS

SULFOSE®

Triple Sulfonamides, Wyeth
(*Trisulfapyrimidines: Sulfadiazine, Sulfamerazine, Sulfamethazine*)

Wyeth®
Philadelphia 1, Pa.

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.

"80% of epileptics... can, with appropriate care and encouragement, lead a normal life"*

* Lord Cohen of Birkenhead: *British M.J.* 1:672, 1958.

for appropriate medical management of epilepsy

the Parke-Davis family of anticonvulsants

...an anti-epileptic for every clinical need

- complete control of seizures in many patients
- reduced incidence and severity of seizures in many others

for grand mal and psychomotor seizures

Dilantin®

Sodium (diphenylhydantoin sodium, Parke-Davis) is supplied in many forms —including Kapseals® of 0.03 Gm. and 0.1 Gm. in bottles of 100 and 1,000.

Phelantin®

Kapseals (Dilantin 100 mg., phenobarbital 30 mg., desoxyephedrine hydrochloride 2.5 mg.), bottles of 100.

for the petit mal triad

Celontin®

Kapseals (methsuximide, Parke-Davis) 0.3 Gm., bottles of 100.

Milontin®

Kapseals (phensuximide, Parke-Davis) 0.5 Gm., bottles of 100 and 1,000. Suspension, 250 mg. per 4-cc. teaspoon, 16-ounce bottles.

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

48388

Hospital practice of infant feeding

Standard one-formula mixture

Normal infant nutrition requires approximately 50 calories per pound of weight. Caloric distribution should be about 15% from protein, 50% from carbohydrates and 35% from fat as formulated for the mixtures in the tables below.

For young infants, a favorable hospital formula consists of a milk and Karo Syrup mixture, isocaloric with human milk, e.g. 20 calories per ounce.

WHOLE MILK FORMULA

FORMULA	OZ.	TOTAL CALORIES	CARB. CAL.	FAT CAL.	PROT. CAL.
Whole milk	24	480	5%	36%	14%
Water	22	—	—	—	—
Karo Syrup	1½	180	45%	—	—

EVAPORATED MILK FORMULA

FORMULA	OZ.	TOTAL CALORIES	CARB. CAL.	FAT CAL.	PROT. CAL.
Evaporated milk	11	484	5%	36%	14%
Water	22	—	—	—	—
Karo Syrup	1½	180	45%	—	—

An infant will usually take 2 to 3 ounces more than his *age in months* at 3 to 4 hour intervals to satisfy his appetite and nutritional needs. It is psychologically unwise to force prescribed amounts. Normally, the gain in weight of 6 to 8 ounces a week during the earlier months gradually diminishes to 3 to 4 ounces a week by the end of the first year. The standard one-formula mixture not only provides adequate nutrition when vitamin supplements are added; it also provides educational opportunities to prevent feeding problems.

ADVANTAGES OF KARO® SYRUP IN INFANT FEEDING

Composition: Karo Syrup is a superior dextrin-maltose-dextrose mixture because the dextrins are nonfermentable and the maltose is rapidly transformed into dextrose which requires no digestion.

Concentration: Volume for volume Karo Syrup furnishes twice as many calories as similar milk modifiers in powdered form.

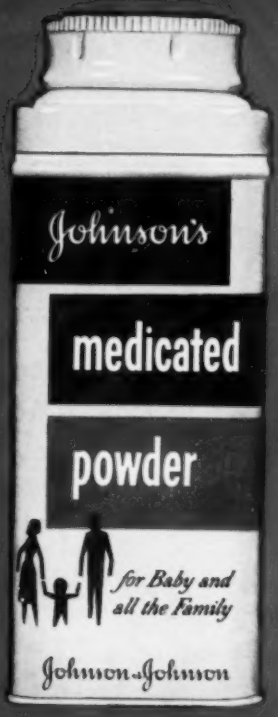
Purity: Karo Syrup is processed at sterilizing temperatures, sealed for complete hygienic protection and devoid of pathogenic organisms.

Low Cost: Karo Syrup costs 1/5 as much as expensive milk modifiers and is available at all food stores.

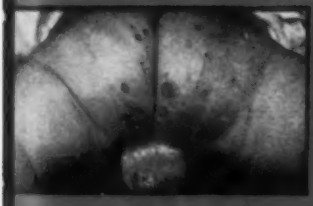
Free to Physicians—Book of Infant Feeding Formulas with convenient schedule pads. Write: Karo Infant Feeding Guide, Box 280, New York 46, N. Y.

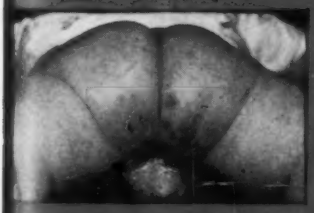
CORN PRODUCTS REFINING COMPANY

NOW... FOR PATIENTS OF ALL AGES



prevents and relieves skin discomforts—aids healing
superior antibacterial action*





Top: Patient R. R.—Severe "diaper rash" with secondary infection at start of treatment, 12/26/56.

Bottom: Eight days after treatment with JOHNSON'S MEDICATED POWDER, 1/3/57. Almost complete clearing of initial rash and of secondary infection.

clinically effective: routine use reduces substantially the incidence of common rashes of infants and young children. Particularly effective in both preventing and modifying the course of "diaper rash" of various etiologies.

twofold antibacterial action: the combination of hexachlorophene and para-chloro-meta-xylenol provides potent antibacterial effect—curbs primary infections, helps prevent secondary infections.

twofold anti-ammonia action: specific inhibition of urease plus antibacterial action against urease-producing bacteria check ammonia formation—prevent diaper rash and ammoniacal dermatitis.

twofold absorbent action: two moisture absorbents combat maceration, chafing, irritation—keep skin cool and dry.

JOHNSON'S MEDICATED POWDER provides unexcelled dry lubrication. Ideal for sensitive skin—completely safe for babies and children.

For free sample, write Johnson & Johnson, New Brunswick, N. J.

*CONTAINS HEXACHLOROPHENE 0.25% PER CENT AND PARA-CHLORO-META-XYLENOL 0.25 PER CENT

Johnson & Johnson
New Brunswick, New Jersey

250,000,

250,000,000 cans
produced with
every care
to merit use
with confidence

,000

This golden can represents the 250,000,000th can of Dextri-Maltose produced. It symbolizes our appreciation to the medical profession for their advancement of infant nutrition and care in the past half-century. And with it we rededicate ourselves to continuing provision of the products and services needed for physician-controlled infant feeding—both for "normal" babies and for those with special feeding problems.

for your use in feeding "normal" babies...
Lactum® (Modified milk formula, Mead Johnson – liquid/"instant" powder). Made from whole milk and Dextri-Maltose. A "classic" modified milk formula, of the type used in feeding millions of babies. Dextri-Maltose® (Maltose-dextrins formula modifier, Mead Johnson – powder). "Professional" carbohydrate – designed specifically for use in infant formulas.

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Symbol of service in medicine

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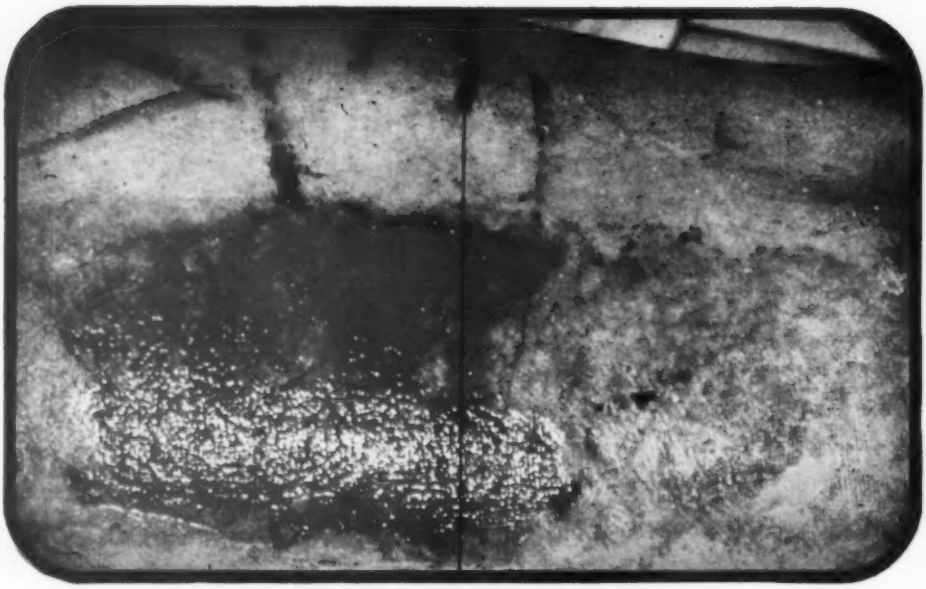


Skin graft donor site after 2 weeks' treatment with ...

petrolatum gauze—still largely granulation tissue | FURACIN gauze—completely epithelialized

OBJECTIVE EVIDENCE OF SUPERIOR WOUND HEALING

was obtained in a quantitative study of 50 donor sites, each dressed half with FURACIN gauze, half with petrolatum gauze. Use of antibacterial FURACIN Soluble Dressing, with its water-soluble base, resulted in more rapid and complete epithelialization. No tissue maceration occurred in FURACIN-treated areas. There was no sensitization.

Jeffords, J. V., and Hagerty, R. F.: Ann. Surg. *145*:169, 1957.

FURACIN®. . . brand of nitrofurazone

the broad-range bactericide that is *gentle to tissues*

spread FURACIN Soluble Dressing: FURACIN 0.2% in water-soluble ointment-like base of polyethylene glycols.

sprinkle FURACIN Soluble Powder: FURACIN 0.2% in powder base of water-soluble polyethylene glycols. Shaker-top vial.

spray FURACIN Solution: FURACIN 0.2% in liquid vehicle of polyethylene glycols 65%, wetting agent 0.3% and water.

EATON LABORATORIES, NORWICH, N.Y.

Nitrofurans—a NEW *class of antimicrobials—neither antibiotics nor sulfonamides*

which women...

and when...

need

iron therapy?

Many clinicians agree that the normal woman of child-bearing age requires iron therapy for a month or six weeks of *each* year.

Iron-deficiency anemia, usually identified as hypochromic microcytic anemia, is seen in most age groups, from the adolescent to the senior members.

For the treatment of these common anemias, Livitamin offers *peptonized* iron—virtually predigested, well absorbed, and less irritating than other forms. The Livitamin formula, which contains the B complex, provides integrated therapy to normalize the blood picture.

Formula: Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} Activity (derived from Cobalamin conc.)	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

LIVITAMIN®

with Peptonized Iron

The S. E. MASSENGILL Company BRISTOL, TENNESSEE • NEW YORK • KANSAS CITY • SAN FRANCISCO

To ensure desired therapeutic response — look to peptonized iron

CURRENT STUDIES* SHOW PEPTONIZED IRON

One-third as toxic as ferrous sulfate.

Absorbed as well as ferrous sulfate.

Non-astringent.

Free from tendencies to disturb digestion. (One-tenth as irritating to the gastric mucosa as ferrous sulfate.)

More rapid response in iron-deficient anemias.

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition *1*:35 (Jan.-Feb., 1957).

Currently, mailings will be forwarded only at your request. Write for samples and literature.

LIVITAMIN®

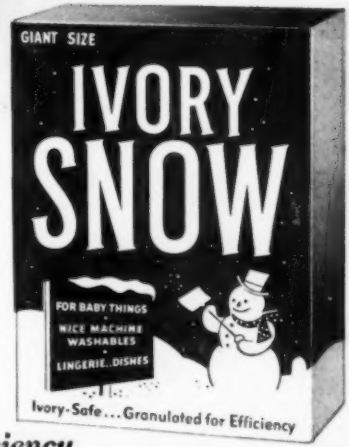
with Peptonized Iron

The S. E. MASSENGILL Company BRISTOL, TENNESSEE • NEW YORK • KANSAS CITY • SAN FRANCISCO

Why should you recommend Ivory Snow for baby's wash?

. **Because it's as safe a soap as a mother can use . . .** leaves diapers and baby clothes soft, gentle-clean . . . and completely ree from irritating deposits that can chafe tender skin!

. **Because it's as practical for mother as it is safe for baby—** he only soap that gives a busy mother Ivory-safety in the fficient granulated form she needs for today's washing machines!



Only Ivory Snow is Ivory-safe and granulated for machine efficiency.

99 44/100% PURE® with Beauty Glow. A PROCTER & GAMBLE PRODUCT

now

Engran

Squibb Multiple Vitamin Drops

Baby Drops

for infants and children up to 4 years of age

- pleasant-tasting *full* vitamin support
- in *half* the volume
- lasts *twice* as long

Engran Baby Drops Contain:

	0.3 cc.
Vitamin A	2500 units
Vitamin D	500 units
Thiamine	0.6 mg.
Riboflavin	1.0 mg.
Nicotinamide	6.0 mg.
Vitamin C	35.0 mg.
Pyridoxine HCl	1.0 mg.
d-Panthenol	2.5 mg.
Vitamin B_{12}	3.0 mcg.

Supply: 15 cc. and 50 cc. bottles. Convenient 'Flexidose' dropper assures accurate dosage.

SQUIBB *Squibb Quality—the Priceless Ingredient*

'ENGRAN' ® AND 'FLEXIDOSE' ARE SQUIBB TRADEMARKS

All are in the picture . . .

baby, mother, and physician

S-M-A provides adequate nutrition for normal health and growth.

S-M-A Service* . . . A specialized program designed to complement the instructions of the physician from the first visits of the expectant mother through the months of infant feeding. The Service includes the beautifully illustrated and informative "Your Baby Book"; a personalized Mother's Gift from you; "Instructions for Care of Mother and Baby."

Additional features of the S-M-A Service include a physician's handbook, "Modern Infant Feeding," for your personal use.

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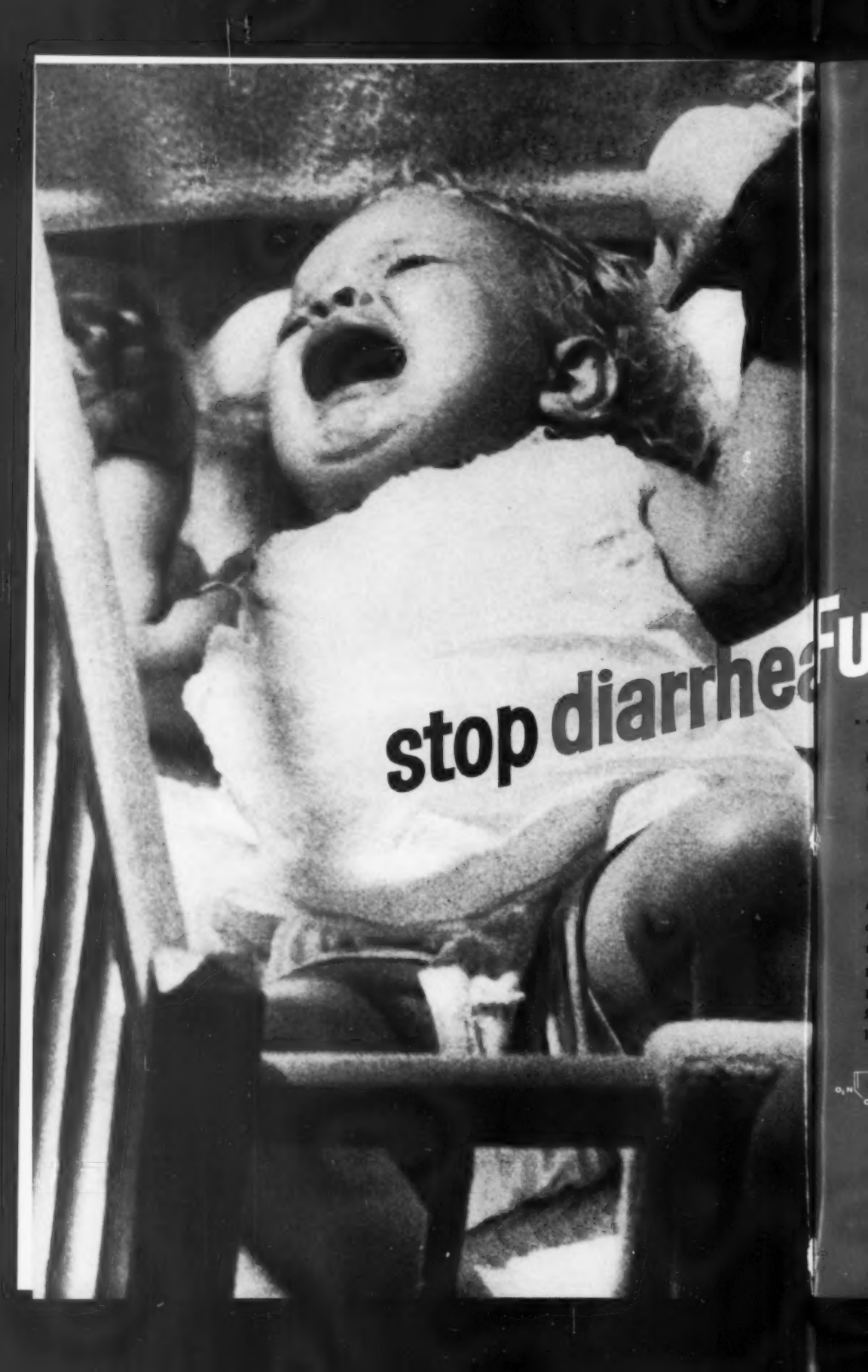
*Available without charge from your Wyeth Territory Manager for all obstetrical patients in your practice.

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.


stop diarrhe

solves acute diarrheal disease problems...

■ swiftly relieves symptoms ■ rapidly destroys bacterial pathogens (bactericidal rather than bacteriostatic) ■ succeeds where others fail against the enteric "problem pathogens" — increasingly prevalent, refractory strains of Staphylococcus, Escherichia, Salmonella and Shigella

Furoxone® Liquid

...without creating new problems

■ does *not* upset the balance of normal intestinal flora
■ does *not* encourage monilial or staphylococcal overgrowth
■ does *not* induce significant bacterial resistance

A PLEASANT ORANGE-MINT FLAVORED SUSPENSION containing FUROXONE, 50 mg. per 15 cc., with kaolin and pectin ■ For patients of all ages (may be mixed with infant formulas, passes through a standard nursing nipple) ■ Dosage: Should provide (in 4 divided doses) 400 mg. daily for adults, 5 mg./Kg. daily for children ■ Supplied: bottles of 240 cc. (also: FUROXONE Tablets, 100 mg. scored, bottles of 20 and 100)

THE NITROFURANS—a unique class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

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a new topically superior

now available

for topical application in dermatotherapy

Kenalog (triamcinolone acetonide) is a new synthetic corticoid compound with powerful anti-inflammatory and antipruritic action. Developed by the Squibb Institute for Medical Research, and evaluated during preliminary clinical trials in over 1,000 patients, Kenalog used topically has demonstrated its greater effectiveness in controlling most common dermatoses.[1] Symptoms of itching and burning are dramatically relieved after topical application of Kenalog.[1,2] A superior agent for both acute and chronic dermatoses, its greater anti-inflammatory action is most clearly apparent in the treatment of chronic, therapeutically refractory conditions, such as chronic eczematous dermatitis.[3] Complete resolution is often obtained with Kenalog where other topically applied steroids have failed.[3]

Kenalog in ointment, cream or lotion form may be used for treatment of a wide variety of dermatoses including:

Atopic dermatitis
Contact dermatitis
Eczematous dermatitis
Neurodermatitis
Seborrheic dermatitis
Insect bites
Pruritus ani
Pruritus vulvae
Lichen simplex chronicus
Exfoliative dermatitis
Stasis dermatitis
Nummular eczema

Kena

SQUIBB Squibb Quality – the Priceless Ingredient

anti-inflammatory steroid

Kenalog safely and effectively provides for prompt symptomatic relief as well as control of many common dermatologic disorders.[1-7]

In double-blind tests in 309 patients comparing 0.1% Kenalog and 1.0% hydrocortisone, Kenalog exhibited superior anti-inflammatory, antiallergic and antipruritic activity.

Investigator	Total Cases	Kenalog Superior	Hydrocortisone Superior	Neither Effective	Equally Effective
Goodman[3]	50	32	3		15
Smith et al.[4]	109	75	3	3	28
Fitzpatrick et al.[5]	120	61	5		54
Lerner[6]	30	20	4	1	5
	309	188	15	4	102

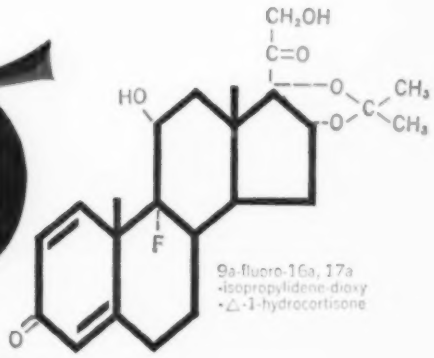
Kenalog is extremely well tolerated locally. No systemic toxicity has been observed in clinical studies, published and in progress, involving over 1,000 patients.[1,3] Metabolic studies show that there is no electrolyte disturbance when Kenalog is applied topically.[1,4,5]

1. Reports to the Squibb Institute for Medical Research.
2. Howell, C. M.: Squibb Clinical Research Notes 1:5 (Oct.) 1958.
3. Goodman, J. J.: Ibid. p. 1.
4. Smith, J. G.; Zawisza, R. J., and Blank, H.: Ibid. p. 6.
5. Fitzpatrick, T.; Crowe, F. W., and Walker, S. A.: Ibid. p. 12.
6. Lerner, A. B.: Ibid. p. 2.
7. Robinson, R. C. V.: Bull. School of Med., U. Maryland 43:54 (July) 1958.

Supply
Kenalog cream, 0.1% – 5 Gm. and 15 Gm. tubes.
Kenalog lotion, 0.1% – 15 cc. plastic squeeze bottles.
Kenalog ointment, 0.1% – 5 Gm. and 15 Gm. tubes.

Kenalog

Triamcinolone Acetonide



9a-fluoro-16a, 17a-isopropylidene-dioxy-Δ-1-hydrocortisone

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safer than aspirin, easier to use

TWO SAFETY FEATURES

1. Salicylamide is well known for its low toxicity index,[1-6] and the fact that it shows little tendency to sensitization.

2. LIQUIPRIN Salicylamide Suspension is supplied in exclusive non-spill safety bottles from which even the most ingenious youngster cannot pour or drink. The medication can only be obtained by using the non-breakable calibrated dropper.

EASY TO USE:

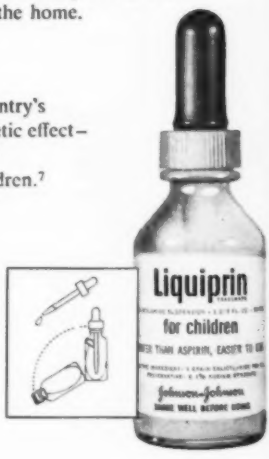
The convenient liquid form permits the required dose to be easily obtained and accurately measured. Children love the pleasant taste—there are no administration problems—even in the home. Blends readily with formula or orange juice.

CLINICALLY EFFECTIVE:

LIQUIPRIN Salicylamide Suspension has been widely tested in several of the country's leading pediatric hospitals and has been found to provide prompt, effective antipyretic effect—especially notable in those cases which do not require specific antibiotic therapy.[7] Proved well tolerated for continued use in studies involving many hundreds of children.[7]

LIQUIPRIN Salicylamide Suspension contains 1 gr. salicylamide per cc. It may be obtained by mothers, at your direction, without prescription.

Recommended dosage: ½ dropper for each year of age, not to exceed 2 droppers (5 gr.). Each ½ dropper contains 1¼ gr. salicylamide.



Johnson & Johnson

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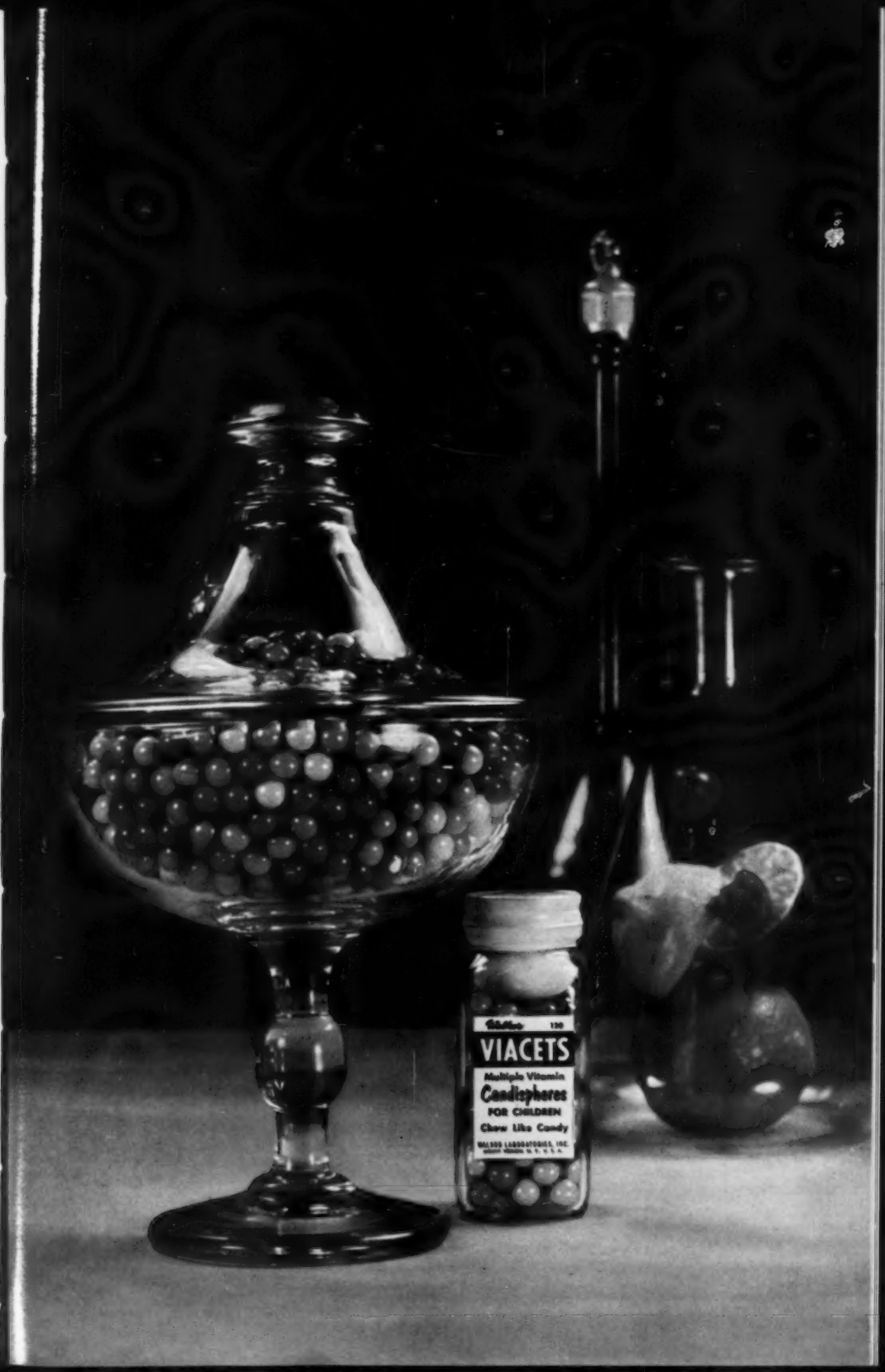
*Trademark for salicylamide suspension, Johnson & Johnson.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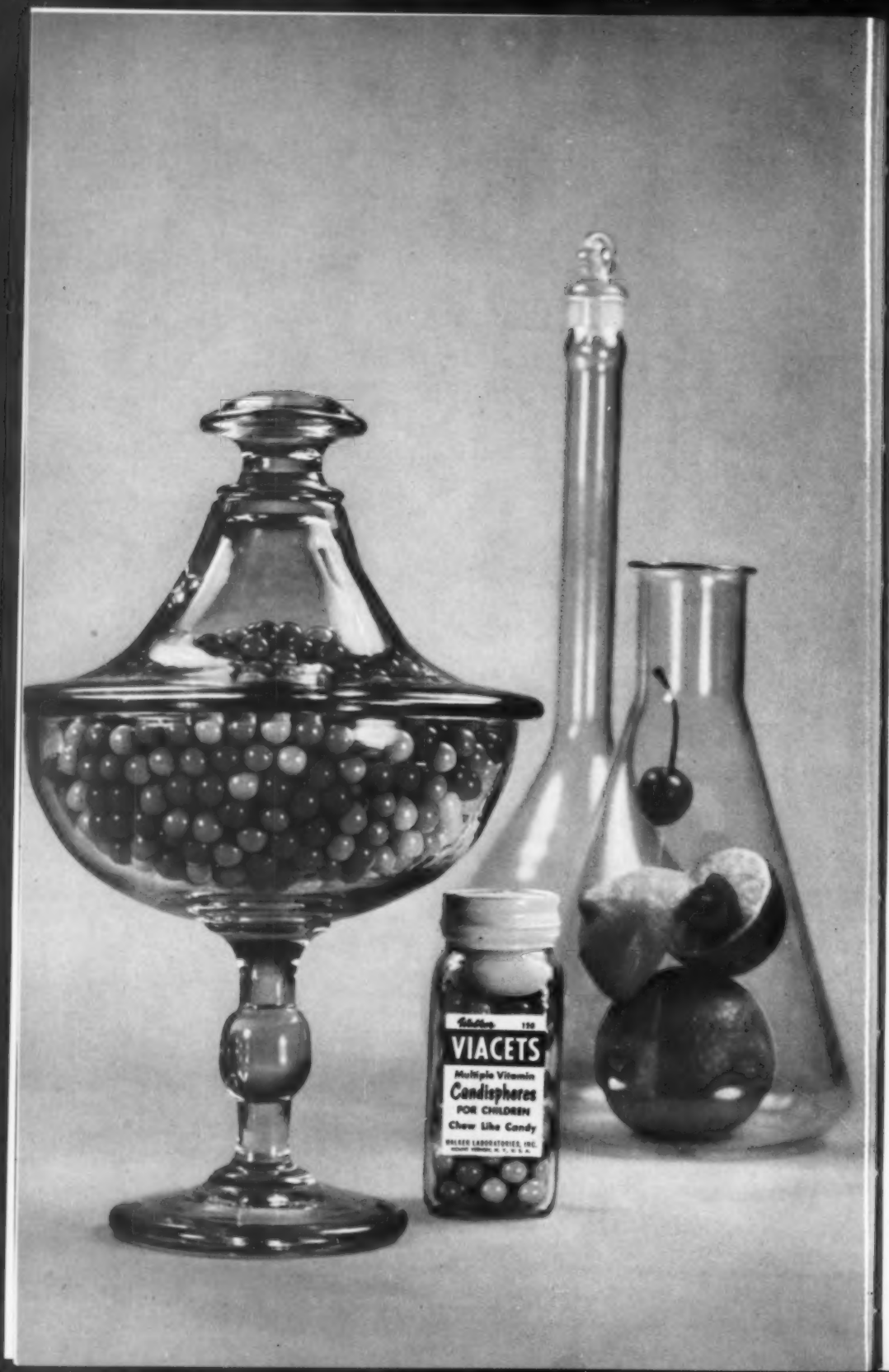
Candispheres
FOR CHILDREN
Chew Like Candy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†Bethell, F. H.: GP 18:97 (July) 1958.

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AUTHORITATIVE diet manuals list Enriched Bread as appropriate for each meal in virtually all therapeutic diets, including restricted fiber, bland, low-fat, high-protein, high caloric, and low caloric diets.

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For relief of symptoms and malaise of the common cold and prevention of secondary complications

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- 3 to 5 times better absorbed, utilized, and stored than from oily media
- deliciously orange-flavored . . . a treat for infants and growing children
- backed by years of clinical study and pediatric application

Dosage: 0.3 to 0.6 cc. daily; may be placed directly on tongue or taken in fruit juices or milk.

Supplied: bottles of 15, 30, and 60 cc. with graduated dropper.

Also available: VIFORT Capsules, bottles of 30 and 100.

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NEW CHERRY-FLAVORED KYNEX* ACETYL

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PEDIATRIC SUSPENSION...

In a wide range of infections caused by sulfa-sensitive organisms, delicious new KYNEX Suspension is fully effective. Therapeutic blood levels are rapidly reached and sustained on one easy-to-take dose a day.

Young patients with urinary tract infections, bacillary dysenteries and many other common disorders, respond readily, improve steadily and before long are back on their feet.

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SUPPLIED: Bottles of 4 fl. oz. Each teaspoonful (5 cc.) of cherry-flavored suspension contains 250 mg. of sulfamethoxypyridazine activity.

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For Ample Air Right Now!

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For quick relief of bronchospasm of any origin. More rapid than injected epinephrine in acute allergic attacks.

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose 0.15 mg. epinephrine.

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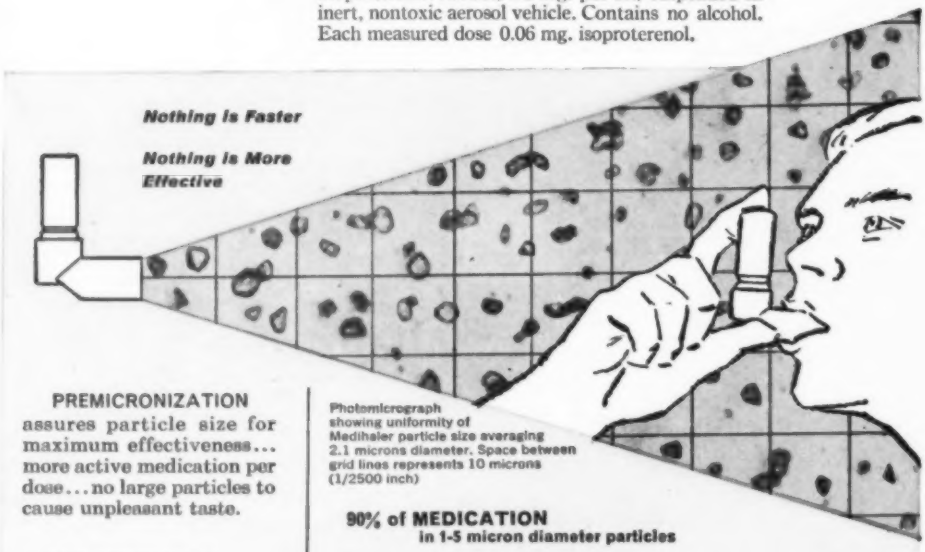
Unsurpassed for rapid relief of symptoms of asthma and emphysema.

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose 0.06 mg. isoproterenol.



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assures particle size for maximum effectiveness... more active medication per dose... no large particles to cause unpleasant taste.

THE MEDIHALER® PRINCIPLE
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Photomicrograph showing uniformity of Medihaler particle size averaging 2.1 microns diameter. Space between grid lines represents 10 microns (1/2500 inch)

90% of MEDICATION
in 1-5 micron diameter particles

99.9% of PARTICLES
in 1-7 micron diameter range

New Improved Premicronized Medihaler suspension
...55 mcg. drug/dose 1-5 microns range

Old type aerosol solution.....	10-12 mcg. drug/dose 1-5 microns range
Squeeze bulb nebulizers.....	2-3 mcg. drug/dose 1-5 microns range

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NOW–*the*

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antibiotic

for any

staph

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KANTREX

Kanamycin Sulfate

Clinically proven bactericidal antibiotic providing:

- *Bactericidal*–not merely bacteriostatic–action
- Wide antimicrobial range...even against many heretofore resistant organisms
- Rapid effect
- High serum levels

–*"leaves the least for the host to do"*

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For rapid bactericidal action in any staph infection...

KANTREX®

Kanamycin Sulfate

"The rapidity with which bacteria are killed by this agent (KANTREX) is reflected by the promptness of the clinical response."[11]

SUMMARY OF CLINICAL RESULTS WITH INTRAMUSCULAR KANTREX —

DISEASE	NUMBER OF PATIENTS	GOOD RESULTS	FAIR RESULTS	UNACCEPTABLE RESULTS	NO RESPONSE OR DIED
[1, 2, 3, 4, 5, 6, 11, 12, 13, 14] Respiratory tract disease	77	53	6	4	12
[1, 2, 3, 4, 5, 6, 11, 13, 14] Urinary tract disease	204	148	—	5	51
[1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 15] Soft tissue infections	177	153	5	4	15
[1, 2, 11, 13, 14, 15] Septicemia	20	10	2	1	7
[1, 2, 3, 4, 5, 11, 13, 14, 15] Osteomyelitis	12	9	—	2	1
[1, 2, 4, 13, 15] Bacterial endocarditis	9	4	2	—	3
[1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 15] Miscellaneous diseases	40	30	4	2	4

— IN 559 CASES REPORTED BY 31 INVESTIGATORS

Indications: Indications for KANTREX include infections due to kanamycin-susceptible organisms, even many of those resistant to other antibiotics:

Respiratory tract infections: Tracheitis, bronchitis, pneumonitis, bronchopneumonia, lung abscess, pleuritis, empyema, and bronchiectasis.

Urinary tract infections: Acute and chronic pyelonephritis, and cystitis.

Soft tissue infections: Wound infections, abscesses, cellulitis.

Blood stream infections.

Osteomyelitis.

Dosage: Adults: Average daily intramuscular dose 1 to 2 Gm. in 2 to 4 equally divided doses.

Children: Average daily intramuscular dose 15 to 30 mg. per Kg. in 2 to 4 equally divided doses.

Precaution:

Skin eruptions and signs of renal irritation (which disappeared on cessation of therapy) have been occasionally noted. In a few cases, signs of eighth nerve dysfunction (tinnitus, vertigo, loss of hearing) have been observed: (1) in patients with pre-existing renal insufficiency, (2) in patients receiving 18 Gm. or more of KANTREX, and (3) in patients over 45 years of age. Animal studies indicate that KANTREX has less auditory toxic potential than dihydrostreptomycin.

Supply: Available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX (kanamycin sulfate) 0.5 Gm. in 2 ml. volume.

KANTREX (kanamycin sulfate) 1.0 Gm. in 3 ml. volume.

Kantrex Sensitivity Discs and comprehensive literature available on request.

References: 1. Bunn, P., Baltch, A., and Krajnyak, O., State University of New York Upstate Medical School, Syracuse, N.Y.: Annals N.Y. Acad. Sci. In press. 2. Cronk, G. A., and Naumann, D. E., Dept. of Health and Preventive Medicine, Syracuse University, Syracuse, N. Y. *Ibid.* 3. Davies, F. G., Marcy State Hospital, Marcy, N.Y. *Ibid.* 4. Dube, A. H., Edward S. Van Duyn Memorial County Hospital, Onondaga, N.Y. *Ibid.* 5. Finegold, S. M., Winfield, M. E., Arcusohn, R. B., Hewitt, W. L., and Guse, L. B., University of California Medical School, Los Angeles, Calif. *Ibid.* 6. Greey, P. H., and Wightman, K. J. R., University of Toronto, Toronto, Can. *Ibid.* 7. Herrold, R. D., and Karabatsos, N., College of Medicine, University of Illinois, Chicago. *Ibid.* 8. High, R. H., Sarris, A., and Huang, N. N., Temple University School of Medicine, Philadelphia. *Ibid.* 9. Ichikawa, T., Medical Faculty, University of Tokyo, Tokyo, Japan. *Ibid.* 10. Katz, S., District of Columbia General Hospital, Washington, D.C.: Personal communication. 11. Rutenburg, A. M., Koota, G. M., and Schweinburg, F. B., Harvard Medical School, Boston: Annals N.Y. Acad. Sci. In press. 12. Ruiz Sanches, F., and Ruiz Sanches, A., University of Guadalajara, Jalisco, Mexico. *Ibid.* 13. White, A., and Knight, V., School of Medicine, Vanderbilt University, Nashville, Tenn. *Ibid.* 14. Yow, E. M., and Monson, O. T., Baylor University College of Medicine, Houston, Tex. *Ibid.* 15. Yow, M. E., and Womack, G. K., Baylor University College of Medicine, Houston, Tex. *Ibid.*

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New vitamin-mineral supplement
in delicious chocolate-like nuggets

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A real treat . . .
the children's favorite . . .
tops with adults, too.

Each nugget contains:

Vitamin A	5,000 Units*
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Vitamin E	2 Units†
Vitamin B-1	2.5 mg.
Vitamin B-2	2.5 mg.
Vitamin B-6	1 mg.
Vitamin B-12 Activity	3 mcg.
Panthenol	5 mg.
Nicotinamide	20 mg.
Folic Acid	0.1 mg.
Biotin	30 mcg.
Rutin	12 mg.
Calcium Carbonate	125 mg.
Boron	0.1 mg.
Cobalt	0.1 mg.
Fluorine	0.1 mg.
Iodine	0.2 mg.
Magnesium	3.0 mg.
Manganese	1.0 mg.
Molybdenum	1.0 mg.
Potassium	2.5 mg.

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Dose: One Nugget per day
Supplied: Boxes of 30—one month's supply
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The great corticosteroid era opened ten years ago with the introduction of Cortone* (Cortisone). Today, MERCK SHARP & DOHME proudly presents the crowning achievement of the first corticosteroid decade—DECADRON (dexamethasone)—a new and unique compound, which brings a new order of magnitude to corticosteroid therapy.

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DEXAMETHASONE

to treat more patients more effectively

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a new order of magnitude

in anti-inflammatory potency

DECADRON "possesses greater anti-inflammatory potency per milligram than any steroid yet produced,"[1] and is "the most potent steroid thus far synthesized."[2] Milligram for milligram, it is, on the average, 5 times more potent than 6-methylprednisolone or triamcinolone; 7 times more potent than prednisone; 28 times more potent than hydrocortisone; and 35 times more potent than cortisone.

in dosage reduction

Thanks to this unprecedented potency, DECADRON is "highly effective in suppressing the manifestations of rheumatoid arthritis when administered in remarkably small daily milligram doses."[3] In a number of cases, doses as low as 0.5-0.8 mg. proved sufficient for daily maintenance. The average maintenance dosage in rheumatoid arthritis is about 1.5 mg. daily.

in elimination and reduction of side effects

Virtual **absence of diabetogenic activity, edema, sodium or water retention, hypertension, or psychic reactions** has been noted with DECADRON.[1,2,3,4] Other "classical" reactions were less frequent and less severe. DECADRON showed no increase in ulcerogenic potential, and **digestive complaints were rare. Nor have there been any new or "peculiar" side effects,** such as muscle wasting, leg cramps, weakness, depression, anorexia, weight loss, headache, dizziness, tachycardia, or erythema. Thus DECADRON introduces **a new order of magnitude in safety,** unprecedented in corticosteroid therapy.

in therapeutic effectiveness

With DECADRON, investigators note "a decided intensification of the anti-inflammatory activity"[3] and antirheumatic potency.[4] Clinically, this was manifested by a **higher degree of improvement** in many patients previously treated with prednisteroids,[3] and by **achievement of satisfactory control in an impressive number of recalcitrant cases.**[3,4]

in therapeutic range

More patients can be treated **more effectively** with DECADRON. Its higher anti-inflammatory potency frequently brings relief to cases resistant to other steroids. Virtual freedom from diabetogenic effect in therapeutic dosage permits treatment of many diabetics without an increase in insulin requirements. Absence of hypertension and of sodium and fluid retention allows effective therapy of many patients with cardiovascular disorders. Reduction in the incidence and severity of many side effects extends the benefits of therapy to numerous patients who could not tolerate other steroids. And a healthy sense of well-being, reported by nearly all patients on DECADRON, assures greater patient cooperation.

References:
1. Boland, E. W.: California Med. 88:417 (June) 1958. 2. Bunim, J. J., et al.: Arthr. & Rheum. 1:313 (Aug.) 1958 3. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., June 21, 1958, San Francisco, Calif. 4. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., June 21, 1958, San Francisco, Calif.

DEXAM

To treat more patients more effectively in all allergic and inflammatory disorders amenable to corticosteroid therapy

DOSAGE AND ADMINISTRATION
With proper adjustment of dosage, treatment may ordinarily be changed over to DECADRON from any other corticosteroid on the basis of the following milligram equivalence:

One 0.75 mg. tablet of Decadron* (dexamethasone) replaces:

one 4 mg. tablet of	one 5 mg. tablet of	one 20 mg. tablet of	one 25 mg. tablet of
methylprednisolone or triamcinolone	prednisolone or prednisone	hydrocortisone	cortisone

SUPPLIED:
As 0.75 mg. scored pentagon-shaped tablets; also as 0.5 mg. tablets, to provide maximal individualized flexibility of dosage adjustment.

Decadron*

DEXAMETHASONE

Detailed literature on DECADRON is available to physicians on request.

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to treat more patients more effectively

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. . . "exactly this dose"

for the young asthmatic

- **terminates even severe attacks—in minutes***
- **makes repeated doses unnecessary—no toxic hazards***
- **is virtually free from gastric distress and other side effects***

Dosage: In children, 0.375 (⅜) cc. per pound of body weight. This amount contains 2.0 mg. theophylline and 0.075 cc. ethyl alcohol.

Multiple spoonful doses are best measured into a glass and taken at one time—without dilution. Although rarely required, dosage may be repeated if necessary after 6 or 8 hours. Other theophylline or ephedrine preparations should not be administered with Elixophyllin.

PEDIATRIC DOSAGE TABLE

Age	Dose	Approx. Household Measure
6 months	2.4 cc.	½ teaspoonful
1 year	4.6 cc.	1 teaspoonful
2½ years	10 cc.	2 teaspoonfuls
4 years	15 cc.	1 tablespoonful
60 lbs.	22.5 cc.	1½ tablespoonfuls
80 lbs.	30 cc.	2 tablespoonfuls
100 lbs.	37.5 cc.	2½ tablespoonfuls
120 lbs.	45 cc.	3 tablespoonfuls

oral ELIXOPHYLLIN

Sherman Laboratories

**A folio of all published studies on request*

Detroit 11, Michigan

White's
Vitamin A & D
Ointment
quickens
healing
in
diaper rash

✻ To treat and prevent diaper rash with WHITE'S VITAMIN A & D OINTMENT —turn baby upside down and cover "bottom" liberally. Skin protection with WHITE'S VITAMIN A & D OINTMENT keeps babies comfortable and happy.
also useful for
eczemas and circumcision dressing in infants, episiotomy wounds, fissured nipples, and routine breast care in mothers.

Available in economical 1½ oz. and 4 oz. tubes, and one pound "nursery jars."
WHITE LABORATORIES, INC. • KENILWORTH, NEW JERSEY

FOR PROMPT UTILIZATION

AND BETTER STORAGE

HOMAGENETS®

The only homogenized vitamins in solid form

Homagenets are unusually palatable—and good taste is especially important to your patients. Of more interest to the physician is the homogenization process. This presents both oil and water soluble vitamins in microscopic particles. Thus the vitamins in Homagenets are better absorbed and utilized—and stored longer.[1] These are definite advantages to your patient.

1. Lewis, J.M., et al.: J. Pediat. 31:496.

THE ADVANTAGES OF HOMAGENETS

- Pleasant, candy-like flavor
- Better absorbed, better utilized
- Excess vitamin dosage unnecessary
- Longer storage in the body
- No regurgitation, no "fishy burp"
- May be chewed, swallowed or dissolved in the mouth.

Homagenets are available in five formulas: Prenatal, Pediatric, Therapeutic, Geriatric and Aoral (brand of vitamin A).

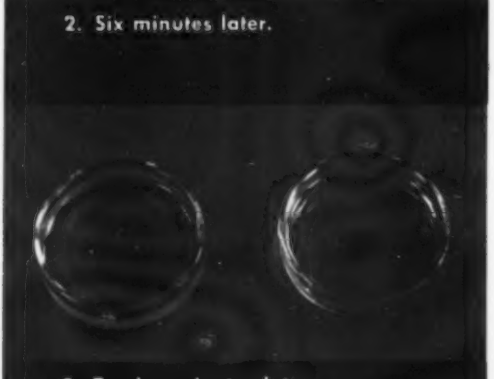
THE S. E. MASSENGILL COMPANY
Bristol, Tennessee

TURN THE PAGE
for laboratory proof of
the prompt dispersion
of Homagenets

VISUAL PROOF OF THE RAPID DISPERSION OF HOMAGENETS®

1. Immediately after placement in Petri dishes.

2. Six minutes later.



3. Twelve minutes later.

4. Two hours and 12 minutes later.

These photographs show the dispersion time of a Homagenet and a soft gelatin capsule in artificial gastric juice at 37°C.

Homagenets are available in five formulas: Prenatal, Pediatric, Therapeutic, Geriatric and Aoral (brand of vitamin A).

Currently, mailings will be forwarded only at your request.
Write for samples and literature.

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE

NEW YORK • KANSAS CITY • SAN FRANCISCO

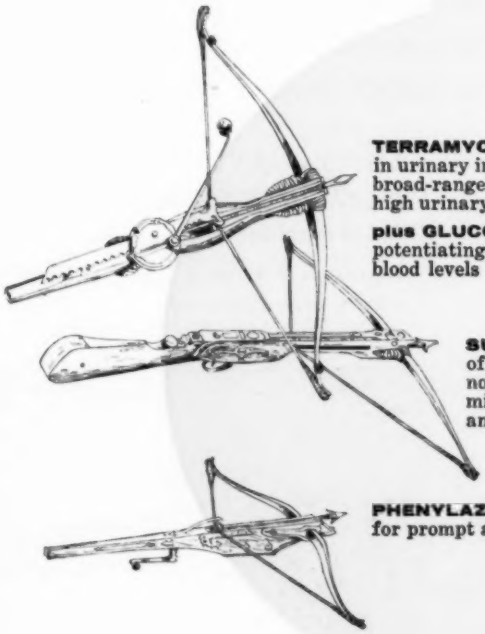
IMPROVE YOUR PATIENT'S CLINICAL PICTURE

in urinary infections

UROBIOTIC*

capsules

A THREE-WAY ATTACK FOR ADDED CERTAINTY



TERRAMYCIN – the antibiotic of choice in urinary infections for almost a decade – broad-range effectiveness, safety, and high urinary concentration.

plus GLUCOSAMINE – a naturally occurring potentiating agent for peak urinary and blood levels of Terramycin.

SULFAMETHIZOLE – the sulfonamide of choice for urinary disinfection; noted for outstanding solubility, minimal acetylation, rapid absorption and proven safety.

PHENYLAZO-DIAMINO-PYRIDINE — for prompt and effective local analgesia.

EACH UROBIOTIC CAPSULE CONTAINS: Cosa-Terramycin (oxytetracycline with glucosamine) 125 mg.; sulfamethizole 250 mg.; phenylazo-diamino-pyridine HCl 50 mg. Supply: Bottles of 50.

DOSAGE: 1-2 capsules four times daily.

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

to pull your diarrhea patients back in shape rapidly

INTROMYCIN
AROBON

two palatable antidiarrheals

FOR IMMEDIATE RELIEF OF SYMPTOMS AND A QUICKER RETURN TO NORMAL

formed stools are produced 5 times faster[1]
lost electrolytes are replenished
water loss is better controlled

AROBON™—*carob powder...demulcent and adsorbent...contains no chemotherapeutics, no sedatives, no narcotics*

Arobon available in 5 oz. bottles.

INTROMYCIN™—*carob powder plus Neomycin and Streptomycin... for infectious diarrheas*

Intromycin available in 2½ oz. bottles.

1. Abella, P. U.: J. Pediat. *41*:182, 1952.

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

for fever and pain / in infants and children

when your little patient

is burning with fever.....

Tempra®

Acetaminophen, Mead Johnson

syrup • drops

brings relief quickly...conveniently

- **safe**
- **well tolerated**
- **easy to give**
- **tastes good**

Mead Johnson

Symbol of service in medicine

TE603

for your pediatric patients...

Sul-Spansion* Liquid

a superior sulfonamide preparation with these important qualities:

1. **efficacy**

   "... an effective form of treatment for acute and chronic bacterial infections ... can be used in place of the more potent antibiotics."[1]

2. **safety**

   "... a safe, readily absorbed, rapidly excreted sulfonamide. ..."[2]

3. **palatability**

   "... palatability of the preparation assured almost universal acceptance by infants and children alike."[3]

4. **q12h convenience**

   "... the sustained release liquid form provides the patient with complete antibacterial protection with only two oral daily doses."[4]

for respiratory and urinary infections...

there is no safer or more effective sulfonamide preparation you can prescribe

1. Dougan, H.T.: The Use of a New Sustained Release Liquid Antibacterial Agent in Pediatrics, Virginia M. Month. *85*:15 (Jan.) 1958.
2. High, R.H.; Huang, N., and Cardenas, N.: Sulfaethylthiadiazole (SETD) in Pediatric Practice, presented as a Scientific Exhibit, Meeting of the New York State Medical Society, New York, N.Y., Feb. 18-21, 1957.
3. Dickstein, B.: Experience with a New Sustained Release Antibacterial Agent in Pediatrics, A Clinical Note, J. Albert Einstein M. Center *5*:114 (Mar.) 1957.
4. Bishoff, R.J., and Mercer, E.H.: A New Sustained Release Antibacterial Preparation in General Practice, presented as a Scientific Exhibit, 106th Annual Meeting of the American Medical Association, New York, N.Y., June 3-7, 1957.

Smith Kline & French Laboratories, Philadelphia

first ⧗ in sustained release oral medication

*Trademark for sustained release sulfaethidole (sulfaethylthiadiazole or SETD), S.K.F.

topical antipruritic potency without greasy stains

FLORINEF-S *Cream*

SQUIBB FLUDROCORTISONE ACETATE WITH SPECTROCIN (NEOMYCIN – GRAMICIDIN)

now, the same efficacy of Florinef-S in a smooth, white vanishing cream

- prompt antipruritic and anti-inflammatory action
- potent antibiotic action against bacterial invaders
- especially well-tolerated and non-irritating; no stain, no grease
- economical: very small amounts are highly effective

Clayman[1] recently treated 60 patients with various inflammatory dermatoses with Florinef-S. All of the 36 patients with contact dermatitis, and 23 of the 24 patients with other inflammatory dermatoses showed marked to satisfactory improvement, especially of the pruritus. The author stated that Florinef-S was "among the most effective medications available for the treatment of contact dermatitis and other inflammatory dermatoses..."

Dosage: Apply Florinef-S Cream lightly and sparingly over the affected areas 2 to 4 times daily.

Supplied: 5-Gm. tubes. Each Gm. of Florinef-S Cream provides 1.0 mg. (0.1%) fludrocortisone acetate, 2.5 mg. neomycin as the sulfate, and 0.25 mg. gramicidin.

Other members of the Florinef-S family: Florinef-S Lotion; Florinef-S Ointment; Florinef-S Ophthalmic Suspension; Florinef-S Ophthalmic Ointment.

Also available: Florinef Lotion and Florinef Ointment.

1. Clayman, S. J.: *J. Med. Soc. N. J.* 55:168 (April) 1958.

SQUIBB *Squibb Quality – the Priceless Ingredient*

'Florinef'® and 'Spectrocin'® are Squibb trademarks.

Choose the right iron

In medicine as in golf, the right iron assures best results!

There is a

MOL-IRON® Tablets / Liquid / Drops

preparation for all orally treatable anemias

For Simple Iron Deficiency Anemia—

MOL-IRON TABLETS **MOL-IRON LIQUID**

Each tablet or teaspoonful contains 195 mg. ferrous sulfate and 3 mg. molybdenum oxide. *Dosage for adults*—2 tablets or 2 teaspoonfuls liquid t.i.d. *For children*—1 tablet or ½ to 1 teaspoonful liquid t.i.d.

Supplied: Tablets—bottles of 100

Liquid—bottles of 12 fl. oz.

For Protection Against Iron Deficiency During Infancy

MOL-IRON DROPS

Especially well tolerated, highly palatable. Each cc. contains 125 mg. ferrous sulfate and 2 mg. molybdenum oxide. *Dosage for children up to 6 years*—0.3 cc. daily; *children more than 6*—0.6 cc. daily.

Supplied: Bottles of 15 cc. and 50 cc. with special dropper.

SUPERIOR TOLERANCE

"Of the 75 patients receiving iron [Mol-Iron] therapy, [only] one was forced to stop treatment...."[1]

OUTSTANDING EFFECTIVENESS

"We have never had other iron salts so efficacious...."[2]

RAPID RESPONSE

"...produced a substantially more rapid therapeutic response than ferrous sulfate, the difference...being statistically significant."[3]

ECONOMICAL THERAPY

Faster maximal hemoglobin response eliminates prolonged treatment.

Costs no more on prescription than ordinary iron salts!

References:

1. Lund, C. J.: Am. J. Obst. & Gynec. *62*:947, 1951. 2. Dieckmann, W. J., and Priddle, H. D.: Am. J. Obst. & Gynec. *57*:541, 1949. 3. Chesley, R. F., and Annitto, J. E.: Bull. Margaret Hague Mat. Hosp. *1*:68, 1948.

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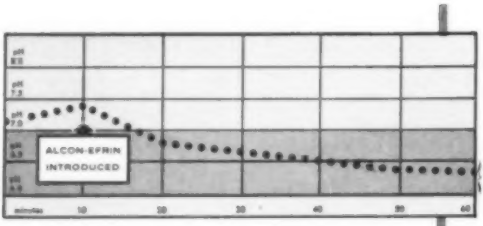
Kenilworth, New Jersey



simply restores nasal breathing.....without sting, burn, irritation or other traditional side-effects

ALCON-EFRIN®
NASAL DECONGESTANT 12
for babies

Phenylephrine HCl 0.16%
Benzalkonium 1:10,000
as wetting agent and preservative;
physiologic nasal pH and tonicity

new brown bottle
adopted may, 1957

In stuffy young noses, from birth to 3 years, ALCON-EFRIN 12 provides simple but effective nasal decongestion without sting, burn, or irritation to delicate tissues.

PROMOTES DRAINAGE—PENETRATING—NON-SENSITIZING

ALCON-EFRIN helps restore the nasal pH to its normal slightly acid range, nature's barrier against pathogens.

SUPPLIED: one-ounce dropper bottles only
ALCON-EFRIN 12, for babies
ALCON-EFRIN 50, extra strength
In 30cc Spray Package and one-ounce dropper bottles
ALCON-EFRIN 25, for children and adults

rhinologic and sterile ophthalmic specialties

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KINNEY PRESENTS

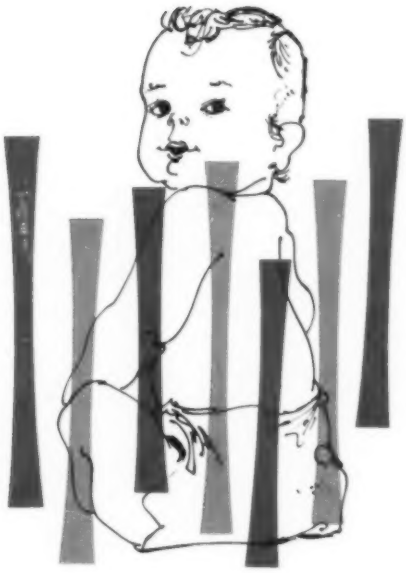
"THE SAFETY-PIN PRINCIPLE" *in pediatric medication*

Particularly in pediatrics, a combination of effectiveness and safety is the true measure of therapeutic value.

EMETROL®
Phosphorated Carbohydrate Solution
a physiologic antiemetic

CHĒL-IRON
Trademark Brand of Iron Choline Citrate
PEDIATRIC DROPS
the new iron
under chelate control

AMMORID®
OINTMENT
and AMMORID®
Diaper Rinse



EFFECTIVE AND SAFE KINNEY EFFECTIVE AND SAFE

FOR FUNCTIONAL VOMITING . . . *a physiologic antiemetic*

EMETROL®

Phosphorated Carbohydrate Solution

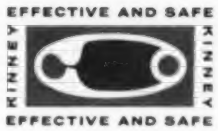
reported effective in 6 out of 7 cases of functional or "epidemic" vomiting, often associated with g.i. virus or intestinal "flu"[1]

usually avoids the need for potentially hazardous antiemetic drugs

often effective with a single dose,[1-3] but may be given as often as needed without danger

specifically effective *only* when the cause of vomiting is functional – thus will not mask serious organic dysfunction requiring more than symptomatic treatment[2]

IMPORTANT: *Must be given undiluted.*



NEW ORAL IRON UNDER CHELATE CONTROL

CHĒL-IRON Pediatric Drops
Trademark Brand of Iron Choline Citrate

an effective hematinic with these additional advantages:

no g.i. irritation – because chelation obviates astringency and precipitation; can even be taken between meals on an empty stomach[4]

safest iron to have in the house – because chelation limits excessive iron uptake providing "a high factor of safety against fatal iron poisoning"[4]

will not stain teeth – because this chelated iron is nonionized

can be added to milk or formula – because chelated iron does not precipitate in the presence of protein or phosphate

Also available: CHĒL-IRON Tablets for older patients

FOR COMMON SKIN IRRITATIONS ... *relief without likelihood of sensitization*

AMMORID® Ointment

a bland, soothing ointment containing benzethonium chloride and zinc oxide

promotes healing of excoriations – helps prevent secondary infection – soothes and softens skin

notably free from allergic sensitization and secondary irritation; avoids "rebound" dermatitis

no risk of "overtreatment reaction" sometimes characteristic of potent topical agents

and AMMORID® Diaper Rinse

useful for safe, continued prophylaxis of diaper rash – inhibits growth of *Bacillus ammoniagenes*–makes diapers soft and odor-free.

PEDIATRIC PRODUCTS OF KINNEY

KINNEY & COMPANY, INC. *Columbus, Indiana*

"the safety-pin principle"

CHARACTERISTIC OF *Kinney*® PEDIATRIC PRODUCTS

EMETROL®

Phosphorated Carbohydrate Solution

Physiologic antiemetic. Clinically documented.[1-3] Contains no sedatives, barbiturates, tranquilizers, or antihistamines. Will not mask possible organic dysfunction.

Dosage: In epidemic vomiting, nausea due to drug therapy, postanesthetic nausea, and other types of functional vomiting – infants and children, 1 or 2 teaspoonfuls at 15-minute intervals until vomiting ceases; adults, 1 or 2 tablespoonfuls at 15-minute intervals until vomiting ceases. If first dose is rejected, resume dosage schedule in 5 minutes.

In "morning sickness" – 1 or 2 tablespoonfuls on arising, repeated every 3 hours or whenever nausea threatens.

Important: DO NOT DILUTE, or permit oral fluids for at least 15 minutes after dose. Dilution alters the stabilized pH necessary for optimal therapeutic effect.

Supplied: In bottles of 3 fl.oz. and 16 fl.oz., containing balanced amounts of levulose and dextrose in coacting association with orthophosphoric acid, the entire preparation stabilized at an optimal pH. Pleasantly mint-flavored.

CHĒL-IRON Pediatric Drops

Trademark — Brand of Iron Choline Citrate

New oral iron under chelate control. Answers the problem of iron toxicity – the "increasing number of near-fatal and fatal poisonings . . . reported after the accidental ingestion of iron by children."[4] Controls diffusion without reducing hematinic efficacy.

Each cc. contains 0.133 Gm. iron choline citrate complex,* equiv. 16 mg. elemental iron, 48 mg. choline base, in flavored nonalcoholic vehicle.

Dosage: Prophylactic – 0.5 cc. daily provides full M.D.R. for infants and children under six. Therapeutic – as directed by the physician.

Supplied: Bottles of 30 cc. with graduated dropper.

(Also available: **Chēl-Iron Tablets**–for adults and older children. Three tablets equiv. 120 mg. elemental iron, 360 mg. choline base. Bottles of 100 tablets.)

AMMORID® Ointment

Contains benzethonium chloride and zinc oxide in pleasantly scented lanolin absorption base, for demonstrated effectiveness with minimal irritation or sensitization.[5]

AMMORID Diaper Rinse often minimizes the need for actual "treatment."

Administration: Wash skin thoroughly, *rinse off all soap,* and apply ointment gently to affected areas. May be used at each diaper change.

Supplied: Two-ounce tubes. *Also:* AMMORID® Diaper Rinse – for prophylaxis of diaper rash. Highly soluble powder containing methylbenzethonium chloride with special water softener. *Supplied:* bottles of 240 Gm. (sufficient for 360 diapers).

REFERENCES: 1. Bradley, J. E., et al.: J. Pediat. 38:41, 1951. 2. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954. 3. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953. 4. Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, 1958. 5. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, Macmillan, 1955, chap. 49.

KINNEY & COMPANY, INC. *COLUMBUS, INDIANA*

*U. S. PATENT 2,575,611

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Again and again, a first choice

for **infection**

- urinary tract infections
- upper respiratory tract infections with bacterial invasion
- mixed infections
- infections not readily diagnosed

for **action**

- attack in depth—both bactericidal and bacteriostatic
- attack in breadth—against many common gram-positive and gram-negative organisms

for **remission**

CONFORMS TO CODE FOR ADVERTISING

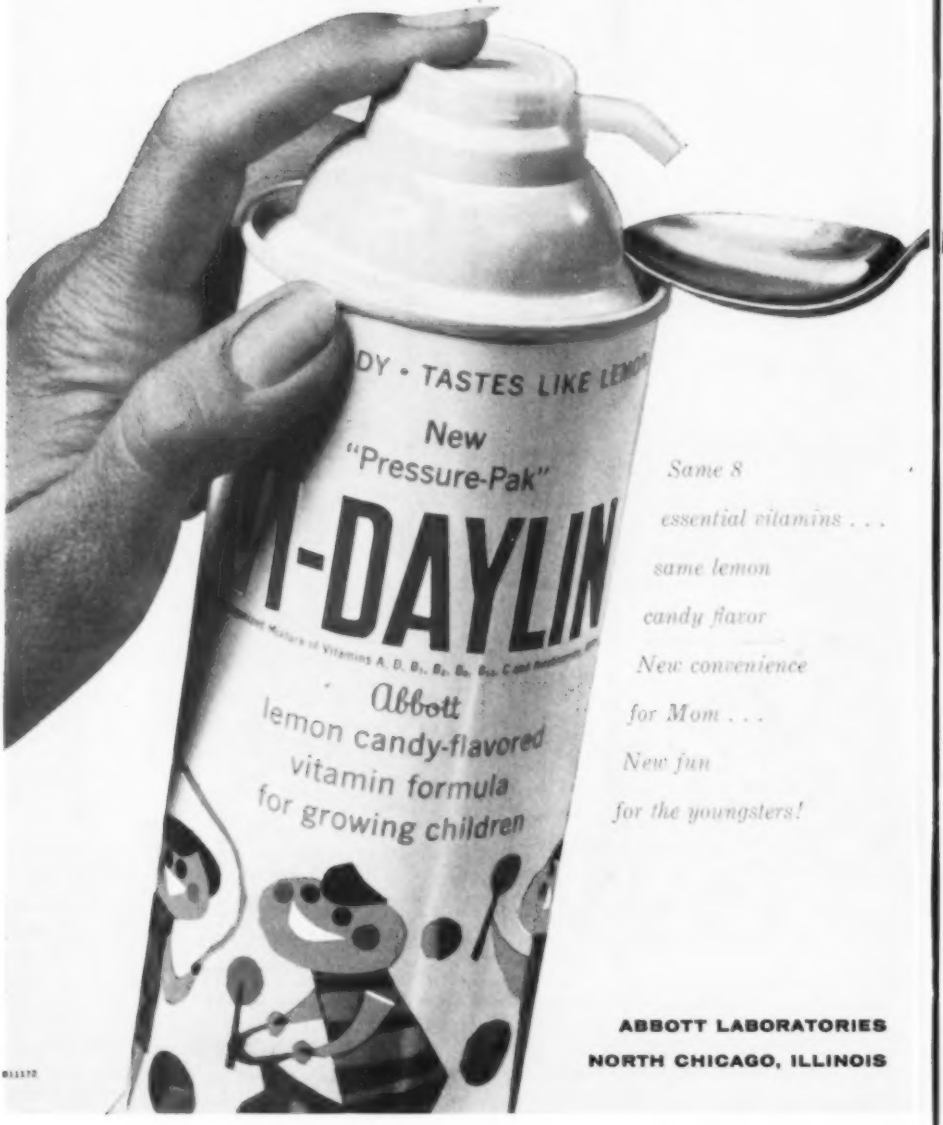
PEN·VEE® SULFAS

Wyeth® Philadelphia 1, Pa.

Tablets: Penicillin V (Phenoxymethyl Penicillin) and Sulfonamides
For Suspension: Benzathine Penicillin V and Sulfonamides

Supplied: Tablets, bottles of 36. For Suspension, bottles of 2 fl. oz. upon reconstitution. Each tablet and 5-cc. teaspoonful contains 125 mg. (200,000 units) of penicillin V (the suspension containing the benzathine salt of penicillin V) and 0.25 Gm. each of sulfadiazine and sulfamerazine.

Now... first children's liquid multivitamin formula in a push-button container



Same 8 essential vitamins . . . same lemon candy flavor

New convenience for Mom . . .

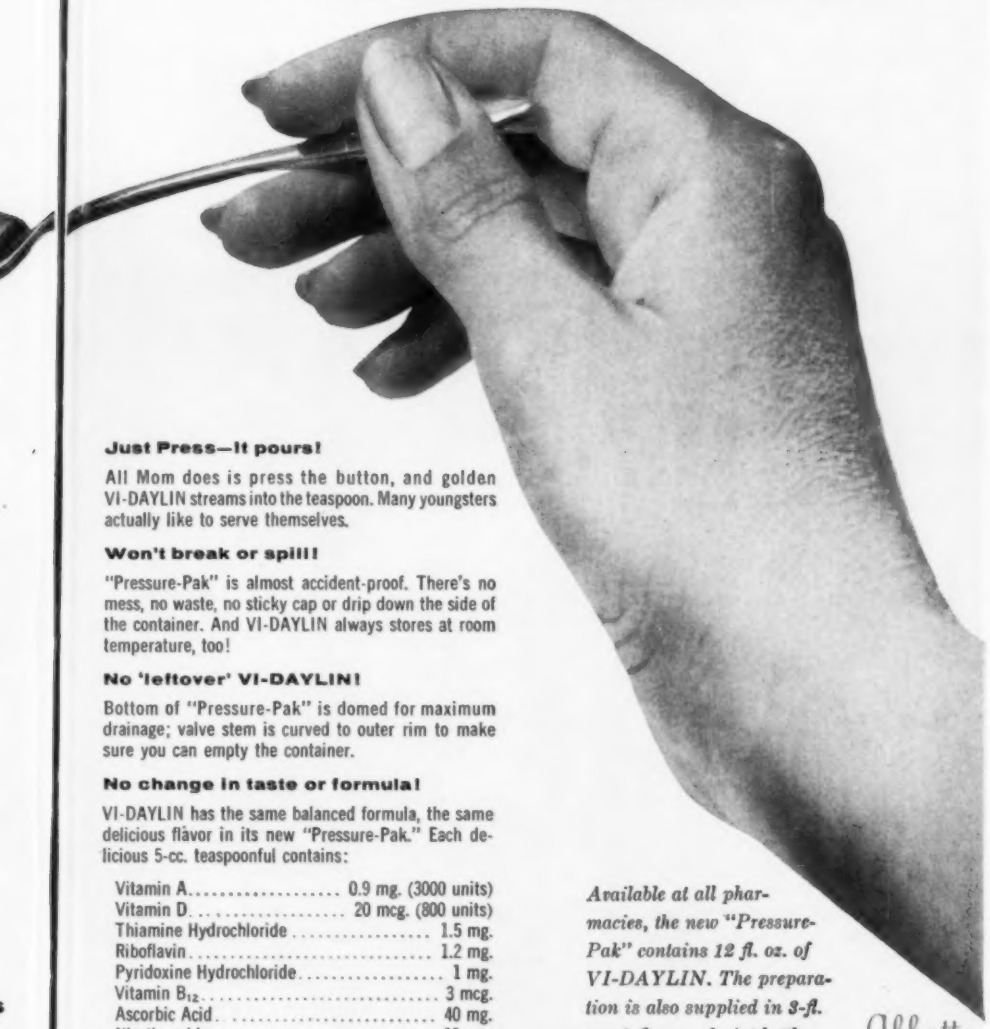
New fun for the youngsters!

ABBOTT LABORATORIES
NORTH CHICAGO, ILLINOIS

VI-DAYLIN®

(Homogenized Mixture of Vitamins A, D, B_1, B_2, B_6, B_{12}, C and Nicotinamide, Abbott)

in the new "Pressure-Pak"



Just Press—It pours!

All Mom does is press the button, and golden VI-DAYLIN streams into the teaspoon. Many youngsters actually like to serve themselves.

Won't break or spill!

"Pressure-Pak" is almost accident-proof. There's no mess, no waste, no sticky cap or drip down the side of the container. And VI-DAYLIN always stores at room temperature, too!

No 'leftover' VI-DAYLIN!

Bottom of "Pressure-Pak" is domed for maximum drainage; valve stem is curved to outer rim to make sure you can empty the container.

No change in taste or formula!

VI-DAYLIN has the same balanced formula, the same delicious flavor in its new "Pressure-Pak." Each delicious 5-cc. teaspoonful contains:

Vitamin A	0.9 mg. (3000 units)
Vitamin D	20 mcg. (800 units)
Thiamine Hydrochloride	1.5 mg.
Riboflavin	1.2 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12}	3 mcg.
Ascorbic Acid	40 mg.
Nicotinamide	10 mg.

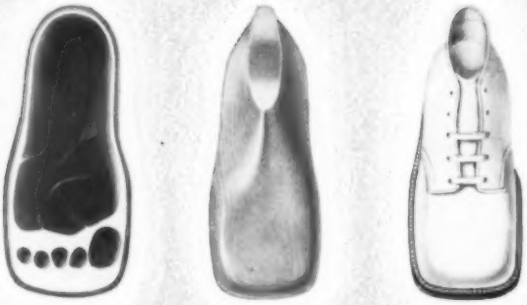
Available at all pharmacies, the new "Pressure-Pak" contains 12 fl. oz. of VI-DAYLIN. The preparation is also supplied in 3-fl. oz., 8-fl.oz. and pint bottles.

Abbott

Child Life provides a

TRUE Straight Last Shoe

No Inflare–
No Outflare



to assist your work with young patients

When young feet need the advantages of Straight Last Construction, CHILD LIFE Straight Last Shoes are readily adaptable to your prescription work.

They allow full freedom for normal foot action and growth . . . provide ample toe room for all toes to grow straight forward. Additionally, these special shoes for children are readily adaptable for all prescribed wedges . . . and are good "follow-through" shoes for corrections already attained. Because of their welt construction, they also lend themselves well to use with Dennis Brown Splints. And, as you can see, CHILD LIFE Straight Last Shoes are styled in the basic popular patterns.

Write for the names of the competent CHILD LIFE dealers in your area.

HERBST Shoe Manufacturing Co., Milwaukee 45, Wis.

NEW

new antibacterial
new chemical entity
new high in effectiveness
new low in side reactions

A NEW BRIGHT SPOT IN ANTIBACTERIAL THERAPY

Madribon

ROCHE

MADRIBON™—brand of 2,4-dimethoxy-6-sulfanilamido-1,3-diazine
ROCHE—Reg. U. S. Pat. Off.

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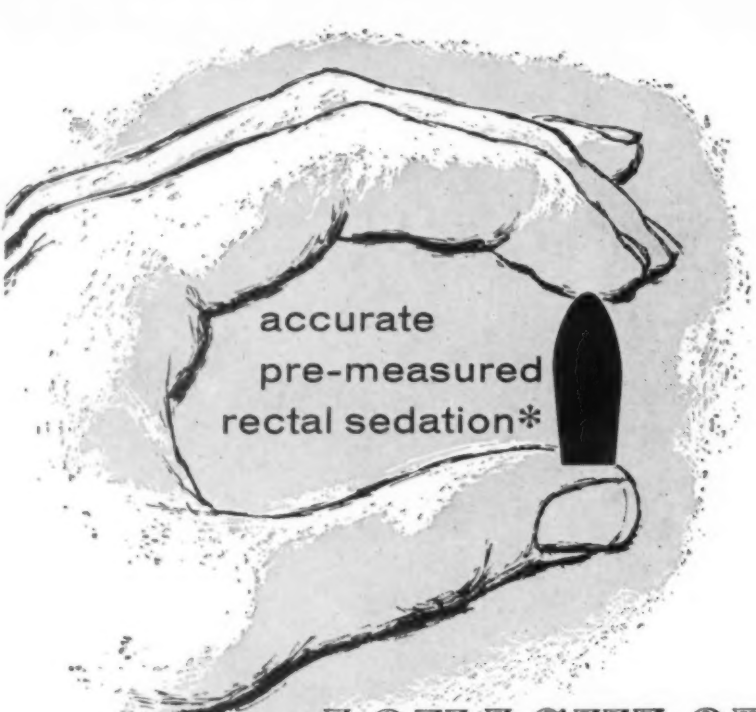

AQUACHLORAL® SUPPRETTES®

CHLORAL HYDRATE
Rectally

SAFE SEDATION
WITHOUT HANGOVER

- Whenever oral therapy is difficult or impossible
- In nausea and vomiting
- To control convulsions
- To quiet hyperexcitability
- Preoperatively
- Postoperatively

The "Neocera" Base
Makes the Difference

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent. *Trademark U.C.C.

Aquachloral Suppettes give *total* drug release within 10 minutes after insertion for prompt sedation. Sedation is accomplished free of gastric or rectal irritation and barbiturate hangover. Rectal administration of Suppettes minimizes careless and excessive use. Dosage is non-cumulative.

Composition: Aquachloral Suppettes contain chloral hydrate in three dosage forms: 5 gr. (0.3 Gm.); 10 gr. (0.6 Gm.); 15 gr. (1.0 Gm.), in Webster's exclusive water-soluble "Neocera" dispersal base.

Supplied: In jars of 12.

Administration and Dosage: Rectally. *Children:* Under 2 years, 0.2 to 0.5 Gm.; 2–6 years, 0.5 to 1.0 Gm.; 6–12 years, 1.0 to 1.3 Gm. *Adults:* 0.6 to 1.2 Gm., as needed.

NO REFRIGERATION NECESSARY **SAMPLES ON REQUEST**

Webster **THE WILLIAM A. WEBSTER COMPANY • MEMPHIS 5, TENNESSEE**

NEW

realistic therapy in pneumonia

A 13-year-old girl with penicillin-resistant pneumonia received an initial dose of 1250 mg Madribon, followed by 625 mg daily. On the third day of Madribon treatment, the temperature returned to normal. X-rays showed marked improvement in the lung fields. She was discharged eight days later.[1]

A NEW BRIGHT SPOT IN ANTIBACTERIAL THERAPY

Madribon

ROCHE

Madribon, a completely new antibacterial, shows wide-spectrum activity against many common gram-positive and gram-negative pathogens, including staphylococci, streptococci, pneumococci, E. coli, klebsiella and listeria.

Low dose, 24-hour action. "The use of Madribon was very simple...."[3] A single, low dose of Madribon produces peak blood concentrations within 4 hours, maintains them at near-constant level for the next 24 hours.[2,4]

Safer. The incidence of side effects with Madribon is less than 3% in more than 5000 cases. Those reported were relatively mild—dizziness, nausea and vomiting. Because Madribon is excreted primarily as a highly soluble glucuronide, there is little likelihood of crystalluria or kidney damage.

MADRIBON T.M. —brand of 2,4-dimethoxy-6-sulfanilamido-1,3-diazine

ROCHE—Reg. U. S. Pat. Off.

ROCHE LABORATORIES • *Division of Hoffmann-La Roche Inc* • *Nutley 10* • *N. J.*

TRANQUILIZER OF CHOICE IN PEDIATRIC PRACTICE

for ***'round-the-clock,*** sustained relief from tension symptoms—sleeplessness, irritability, apprehension, headache[1]—on q. 12 h. medication

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meprobamate (Miltown®) **continuous release** capsules

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1. Baird, H. W., III: A comparison of Meprospan (sustained action meprobamate capsule) with other tranquilizing and relaxing agents in children. Submitted for publication, 1958.

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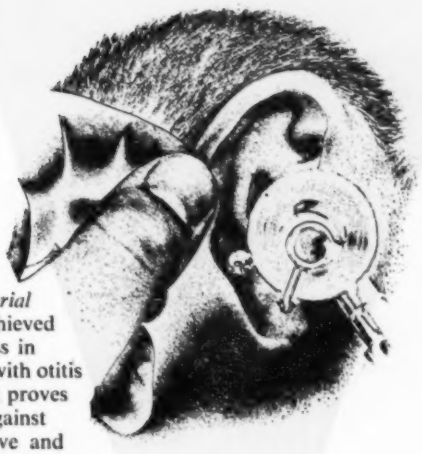

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realistic therapy in respiratory infections

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References: 1. E. H. Townsend and A. Borgstedt, Paper read at the Sixth Annual Symposium on Antibiotics, Washington, D.C., October 15-17, 1958.

2. S. Ross, J. R. Puig and E. A. Zaremba, Paper read at the Sixth Annual Symposium on Antibiotics, Washington, D.C., October 15-17, 1958.

3. W. A. Leff, Paper read at the New Jersey Chapter of the American Federation for Clinical Research, East Orange, N. J., September 17, 1958.

4. W. P. Boger, Paper read at the Sixth Annual Symposium on Antibiotics, Washington, D.C., October 15-17, 1958.

A NEW BRIGHT SPOT IN ANTIBACTERIAL THERAPY

Madribon

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DOSAGE		TABLETS		SUSPENSION (teasp.)	
		initially	q. 24 h.	initially	q. 24 h.
ADULTS:		2	1	4	2
CHILDREN:	20 lbs	½	¼	1	½
	40 lbs	1	½	2	1
	80 lbs	2	1	4	2

The above dosage should be doubled in severe infections requiring more intensive therapy. Continue therapy for 5 to 7 days, or until patient is asymptomatic for at least 48 hours.

Tablets, 0.5 Gm
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* J.A.M.A. 166: 158, 1958
WELSH, A.L. and EDE, M.
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REFERENCES: 1. Bleiberg, J.: J. M. Soc. New Jersey *55*:371, 1956; 2. Clyman, S. G.: Postgrad. Med. *21*:309, 1957; 3. Bleiberg, J.: Am. Practitioner *8*:1404, 1957; 4. Abrams, B. P. and Shaw, C.: Clin. Med. *5*:839, 1956.

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Foland, J. P.: Bronkephrine in the Management of Bronchial Asthma, Postgrad. Med. 18:307 (Nov.) 1955.

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*Howland, W. S.: Cardiovascular and Clotting Disturbances during Massive Blood Replacement, Anesthesiology 19 (2): 140-152 (March-April, 1958).

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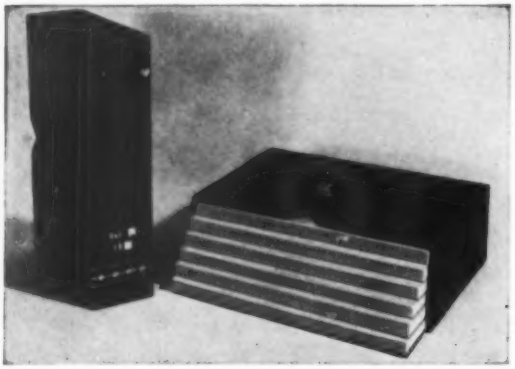

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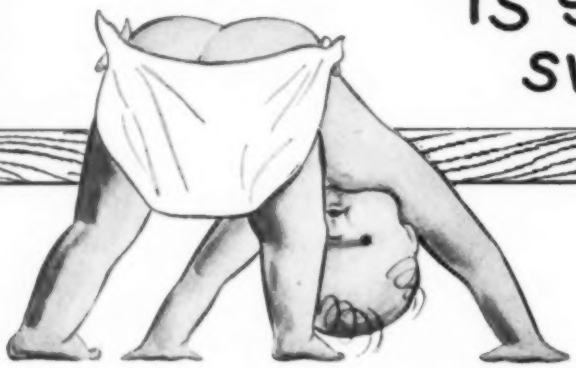

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	Calories from Fat	Calories from Protein
in the average American dietary	1	0.3
in beef rump roast	1	1.27
in beef flank steak	1	1.42
in lamb leg roast	1	1.55
in pork loin chop (lean portion only)	1	1.36
in cured ham	1	1.04
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*Leverton, R.: The Fat, Protein, and Calorie Value of Cooked Meats. Proc. 9th Research Conf. sponsored by the Council on Research of the American Meat Institute, University of Chicago, March 1957.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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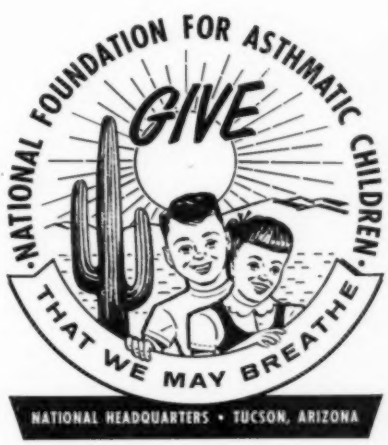

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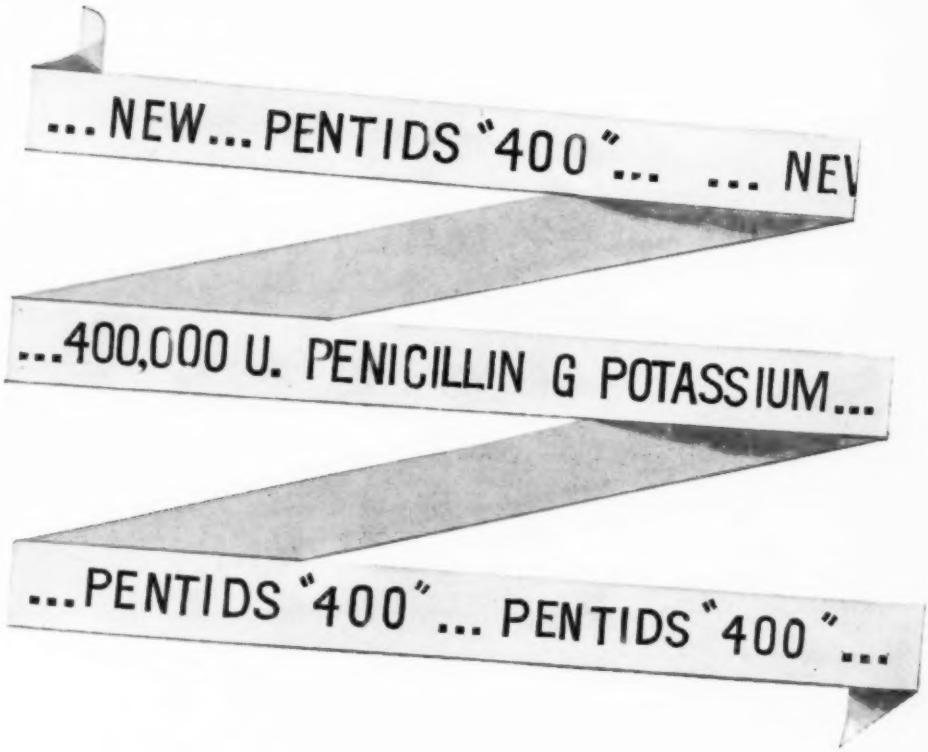

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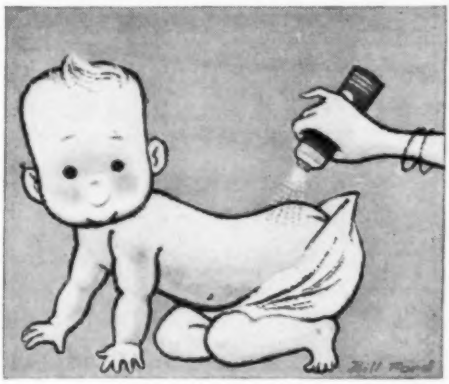

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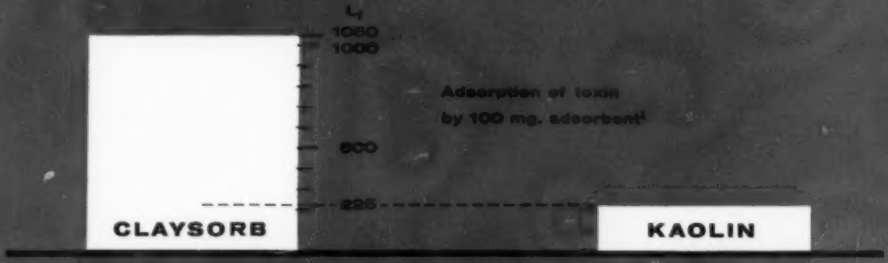

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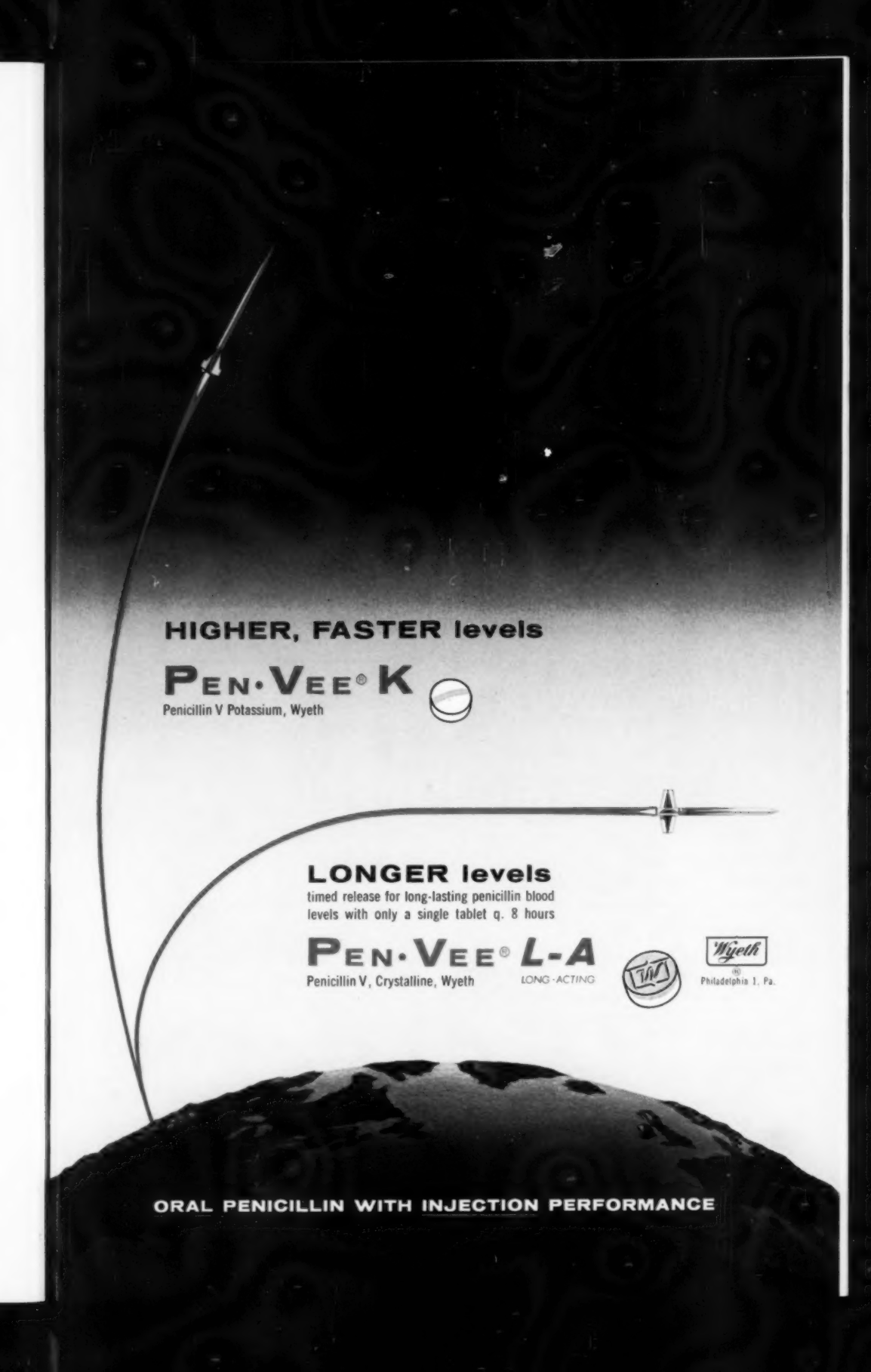
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1. Allen, F. P., Jr.: J. Ped. 46: 155, 1955.

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Arnar-Stone Laboratories, Inc. (Silicote) 84
Articles to Appear 2
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Burroughs Wellcome & Company (U.S.A.), Inc. (Antepar) 50

Center Laboratories, Inc. (Allergy Service) 90
Chicago Pharmacal Company (Katrasul & Vermizine) .. 99
Christmas Seals 98
Ciba Pharmaceutical Products (Serpasil) 20
Ciba Pharmaceutical Products (Pyribenzamine) 87
Corn Products Refining Company (Karo Syrup) 28

Desitin Chemical Company (Ointment) 18
Desitin Chemical Company (Powder) 89
Dome Chemicals, Inc. (Acid Mantle) 92

Eaton Laboratories (Furacin) 32
Eaton Laboratories (Furoxone Liquid) 36, 37
Endo Laboratories, Inc. (Vifort Drops) 46

Florida Citrus Commission 11
Fuller Pharmaceutical Company (Tucks) 90

Herbst Shoe Manufacturing Company (Child Life Shoes) 68
Hoffmann Laboratories, Inc. (B.A.C.) 12
Hyland Laboratories (Antihemophilic Plasma) 88

Irwin, Neisler & Company (Rynatan) 14, 15

Johnson & Johnson (Medicated Powder) 29
Johnson & Johnson (Liquiprin) 40
Johnson & Johnson (Nose Drops & Spray) 85
Jones & Hauck Box Corps., Jesse (Volume File) 88

Kannenglesser & Company (Kanana Banana Flakes) .. 74
Kinney & Company, Inc. (Emetrol, Chel-Iron & Ammorid) ..... Insert between pp. 64 and 65

Lakeside Laboratories (Imferon) 41
Landers, Frary & Clark Subsidiary Electric Steam Radiator Corporation (Vaporizer) 107
Lederle Laboratories, a Division of American Cyanamid Company (Kynex) 47
Lederle Laboratories, A Division of American Cyanamid Company (Achromycin) 77
Leeming & Company, Inc., Thos. (Piperazate Wafers) 5
Lilly and Company, Eli (V-Cillin K) 82

Maltbie Laboratories Division Wallace & Tiernan, Inc. (Caldesene) 3
Massengill Company, The S. E. (Livitamin) ..... Insert between pp. 32 and 33
Massengill Company, The S. E. (Homagenets) ..... Insert between pp. 56 and 57
Mead Johnson & Company (Fer-In-Sol) 13
Mead Johnson & Company (Vi Sols) ..... Insert between pp. 24 and 25
Mead Johnson & Company (Dextri-Maltose 30, 31
Mead Johnson & Company (Tempra) 59

Merck & Company, Inc. (Codeine) 94
Merck Sharp & Dohme (Redisol) 17
Merck Sharp & Dohme (Cremomycin) 24
Merck Sharp & Dohme (Decadron) 51, 52, 53, 54

National Foundation for Asthmatic Children 95

Parke, Davis & Company (Dilantin, Phelantin, Celontin & Milontin) 26, 27
Parke, Davis & Company (Paladac) 43
Pet Milk Company (Evaporated Milk) 83
Pfizer Laboratories, Div. Chas. Pfizer & Company, Inc. (Bonamine) 9
Pfizer Laboratories, Div. Chas. Pfizer & Company, Inc. (Cosa-Tetracyn) 44, 45
Pfizer Laboratories, Div. Chas. Pfizer & Company, Inc. (Urobiotic) 57
Pitman-Moore Company (Intromycin Arobon) 58
Pitman-Moore Company (Neo-Polycin) 79
Pitman-Moore Company (Novahistine Elixir) 96
Pitman-Moore Company (Novahistine-DH) 97
Procter & Gamble Company (Ivory Snow) 33
Pyramid Rubber Company (Evenflo) 100

Reed & Carnrick (Tarcortin & Neo-Tarcortin) 81
Rhinopto Company (Rhinall Cough Syrup) 102
Riker Laboratories (Medihaler-EPI & Medihaler-ISO) 48
Roche Laboratories, Div. Hoffmann-La Roche, Inc. (Vi-Penta) ..... Second Cover
Roche Laboratories, Div. Hoffmann-La Roche, Inc. (Madribon) 69, 71, 73, 75
Ross Laboratories (Booklet) 103

Schering Corporation (Corilin) 21
Schering Corporation (Coricidin Syrup & Medilets) ..... Insert between pp. 8 and 9
Sherman Laboratories (Elixophyllin) 55
Smith-Dorsey, a division of The Wander Company (Trisulfaminic) 16
Smith Kline & French Laboratories (Thorazine) 10
Smith Kline & French Laboratories (Sul-Spansion Liquid) 60
Smith Kline & French Laboratories (Troph-Iron) 114
Squibb & Sons, E. R. (Mysteclin-V) 1
Squibb & Sons, E. R. (Engran Baby Drops) 34
Squibb & Sons, E. R. (Kenalog) 38, 39
Squibb & Sons, E. R. (Florinef-S) 61
Squibb & Sons, E. R. (Theragran Junior) 91
Squibb & Sons, E. R. (Pentids) 101
Swift & Company (Meats for Babies) 80

Walker Laboratories (Viacets) ..... Insert between pp. 40 and 41
Wallace Laboratories (Meprospan) 72
Webster Company, The William A. (Aquachloral Supprettes) 70
Webster Company, The William A. (Gentian-EV Supprettes) 112
Westwood Pharmaceuticals (Fostex) 8
Westwood Pharmaceuticals (Lowila Cake) 94
White Laboratories, Inc. (Orabiotic) 23
White Laboratories, Inc. (Delectavites) 49, 95, 102
White Laboratories, Inc. (Vitamin A and D Ointment) 56, 99
White Laboratories, Inc. (Mol-Iron) 62, 63
White Laboratories, Inc. (Cod Liver Oil Concentrate Tablets) 105
Winthrop Laboratories (Neo-Synephrine) 19
Wyeth Laboratories (Phenergan) 22
Wyeth Laboratories (Sulfose) 25
Wyeth Laboratories (S-M-A) 35
Wyeth Laboratories (Pen-Vee Sulfas) 65
Wyeth Laboratories (Polymagma) 109
Wyeth Laboratories (Pen-Vee K & Pen-Vee L-A) 111

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

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CONTENTS FOR DECEMBER, 1958

Recognition and Treatment of Adrenal Crises in the Newborn Infant. Robert G. Scherz, Captain, MC, USA, and Leo J. Geppert, Colonel, MC, USA ---- 645

The Circulating Eosinophil Level in the Newborn Infant Following Normal and Difficult Labor. Mostafa Khalil, D.C.H., M.D., Alexandria, Egypt ---- 662

The Use of Deanol in the Treatment of Disorders of Behavior in Children. Leon Oettinger, Jr., M.D., San Marino, Calif. ---- 671

Oleandomycin, a Laboratory and Clinical Evaluation. Richard Koch, M.D., and Lyal D. Asay, M.D., Los Angeles, Calif. ---- 676

Glycogen Storage Disease. Richard Wagner, M.D., Norma Meyerriecks, and Rose Sparaco, Boston, Mass. ---- 683

The Role of Candida Albicans in the Common Skin Disorders of Infancy and Early Childhood. Alfred J. Vignec, M.D., New York, N. Y. ---- 692

Acute Gastroenteritis. James G. Armstrong, M.A., M.B., B.Ch. (Oxon.) Toronto, Canada ---- 704

Empyema in Children. Basil Lionakis, M.D., Stephen W. Gray, Ph.D., John E. Skandalakis, M.D., and W. A. Hopkins, M.D., Atlanta, Ga. ---- 719

Celiac Disease: Response to a Gluten-Free Diet. Stanley N. Graven, Captain, USAF (MC), and Edward J. Tomsovic, Major, MC, USA, Tacoma, Wash. ---- 726

Cerebral Arteriovenous Fistula Producing Cardiac Failure in the Newborn Infant. Adrian Q. Pollock, M.D., and Patricia A. Laslett, M.B., B.S. (London), Louisville, Ky. ---- 731

Methemoglobinema Associated With Intestinal Strangulation Obstruction in the Newborn Infant. Warren W. Quillian, M.D., James W. Lancaster, M.D., and H. Clinton Davis, M.D., Miami, Fla. ---- 737

Coproliths (Calcified Appendiceal Calculi) in Children. Frank C. Stiles, M.D., Monroe, Wis. ---- 741

Clinical Pathological Conference

The Children's Medical Center, Boston, Mass. ---- 744

Comments on Current Literature

Neurologic Complications of Asian Influenza. Russell J. Blattner, M.D., Houston, Texas ---- 751

News and Notes

News and Notes ---- 754

Books

Books ---- 756

Editor's Column

Hail and Farewell ---- 761

Tranquilizers ---- 764

Index

Index ---- 767

(Editorial and Business Communications on page 4)

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